Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

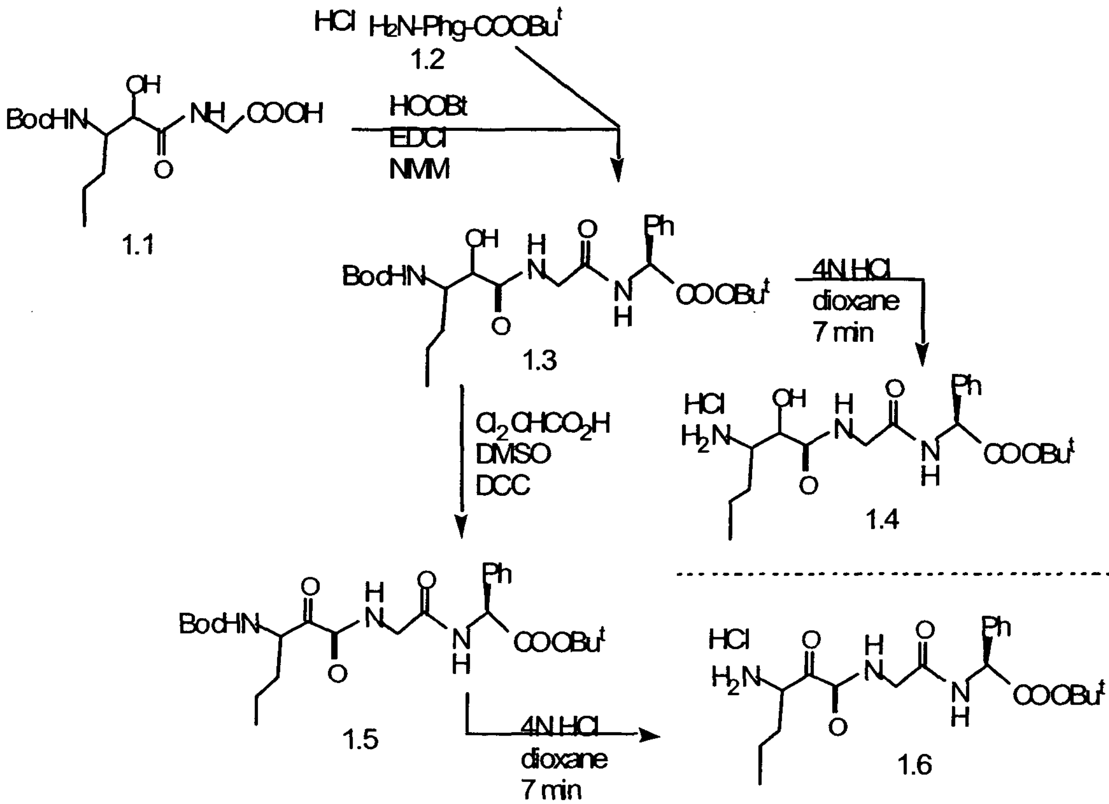
DMAP: 4-N,N-Dimethylaminopyridine

Bop: Benzotriazol-1-yl-oxy-tris(dimethylamino)hexafluorophosphate

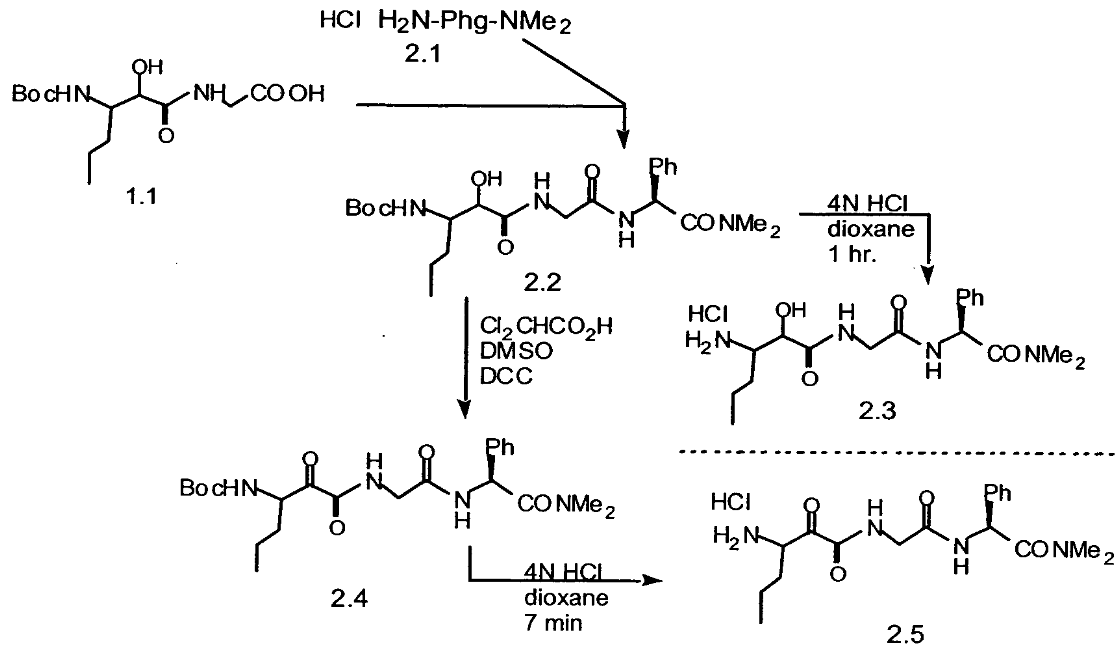
General Preparative Schemes:

The following schemes describe the methods of synthesis of intermediate building blocks:

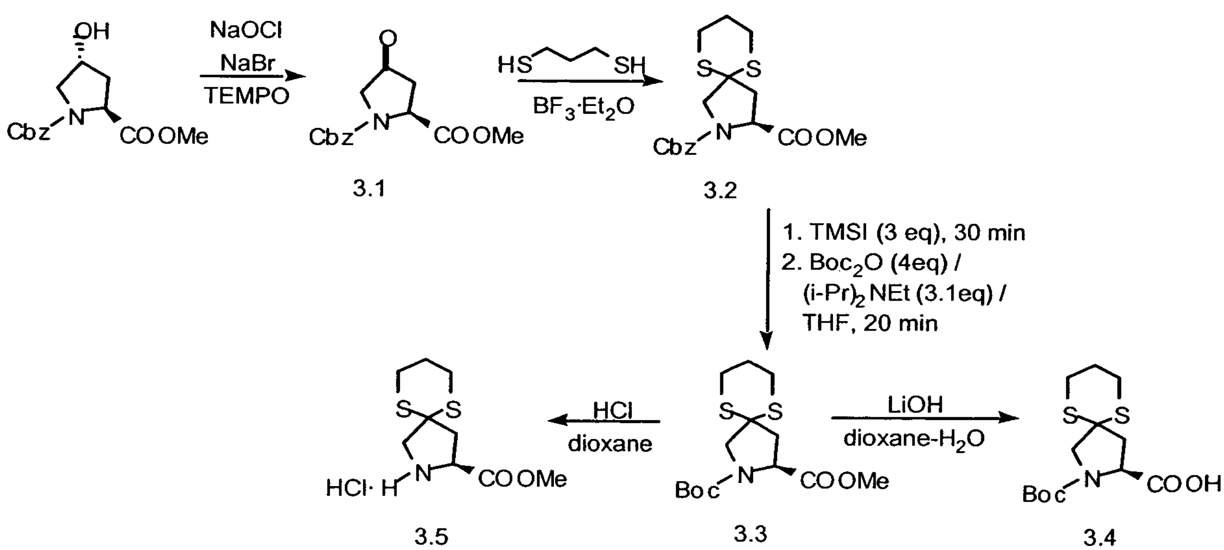
SCHEME 1


HCl H2N-Phg-COOBu^t
1.2
HOOBt
EDCl
NMM
1.1
1.3
4N HCl
dioxane
7 min
1.4
Cl2CHCO2H
DMSO
DCC
1.5
4N HCl
dioxane
7 min
1.6

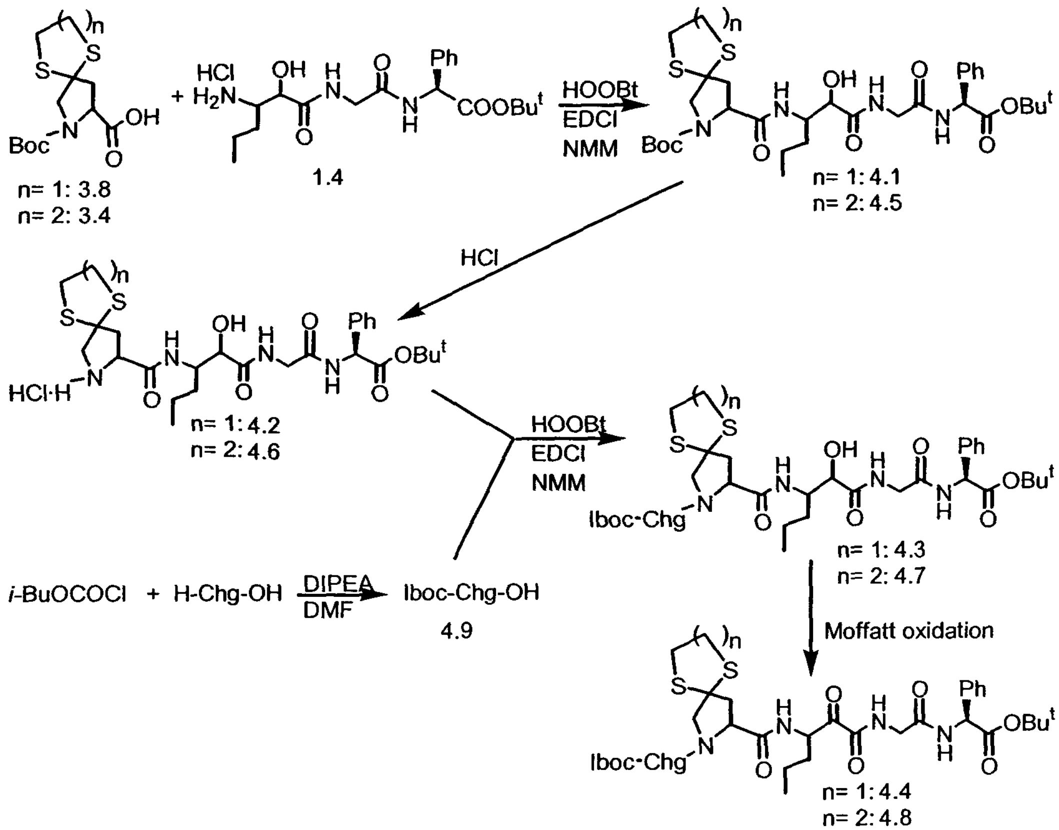
SCHEME 2



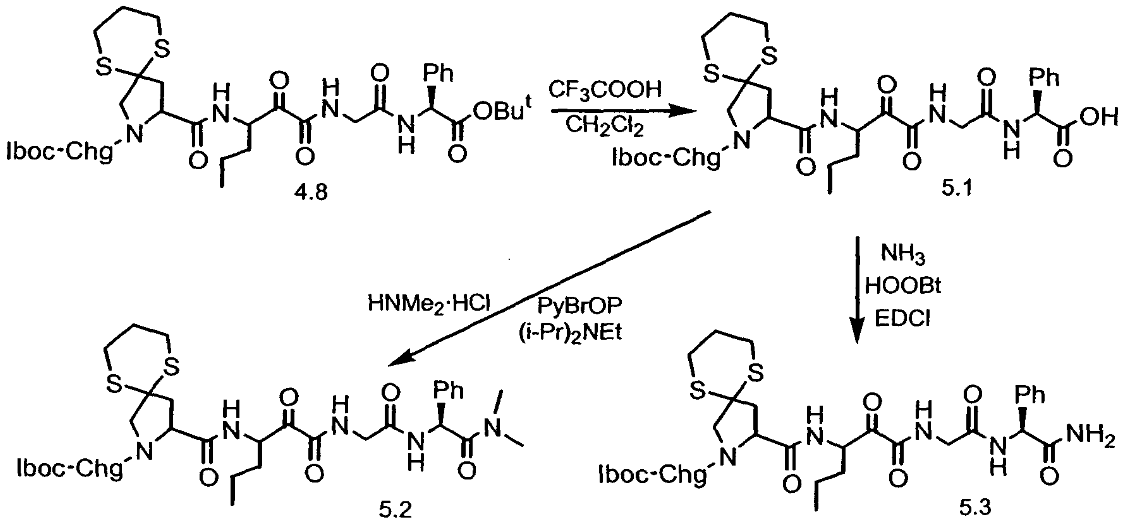
SCHEME 3



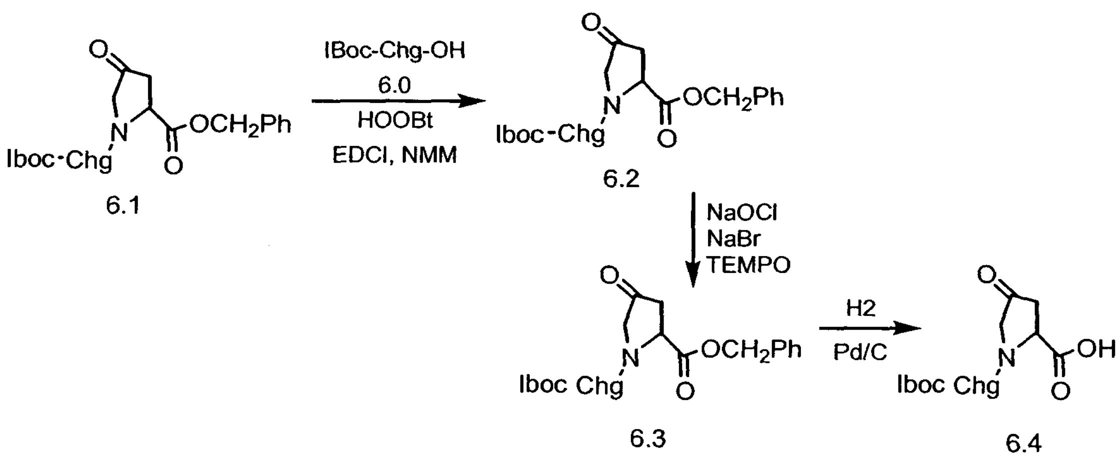
SCHEME 4


n= 1: 3.8
n= 2: 3.4
1.4
HOOBt
EDCI
NMM
n= 1: 4.1
n= 2: 4.5
HCl
n= 1: 4.2
n= 2: 4.6
HOOBt
EDCI
NMM
n= 1: 4.3
n= 2: 4.7
i-BuOCOCl + H-Chg-OH
DIPEA
DMF
Iboc-Chg-OH
4.9
Moffatt oxidation
n= 1: 4.4
n= 2: 4.8

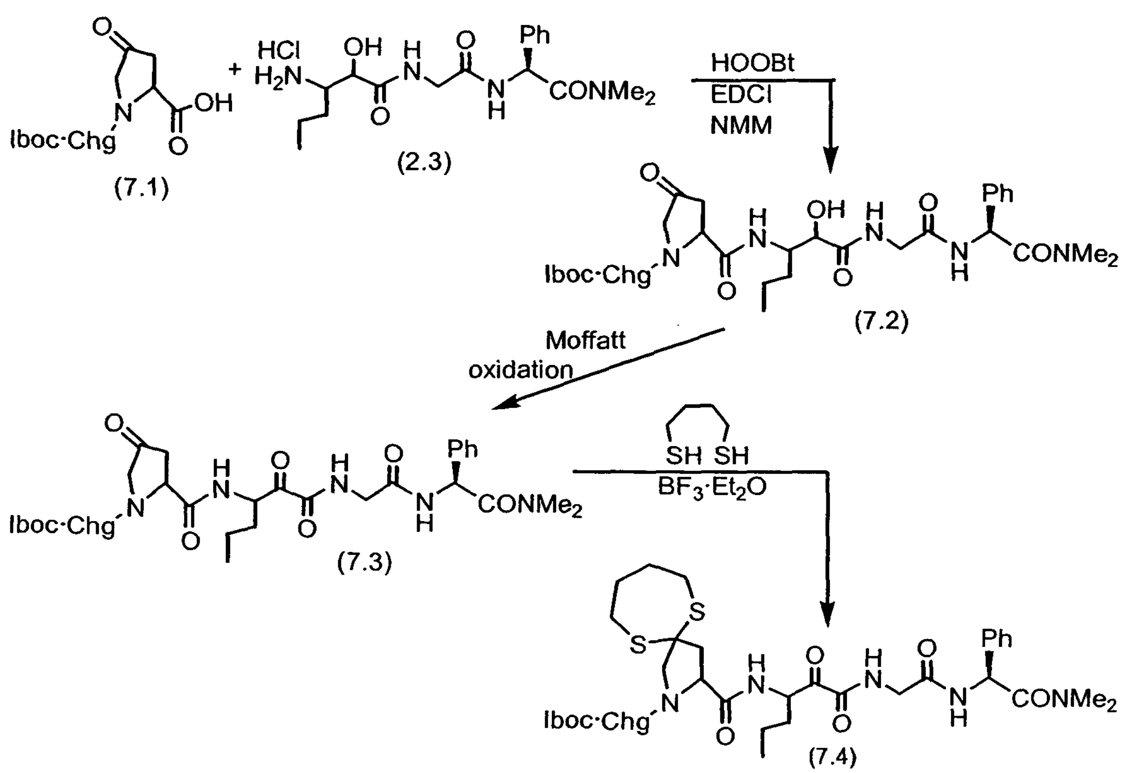
SCHEME 5



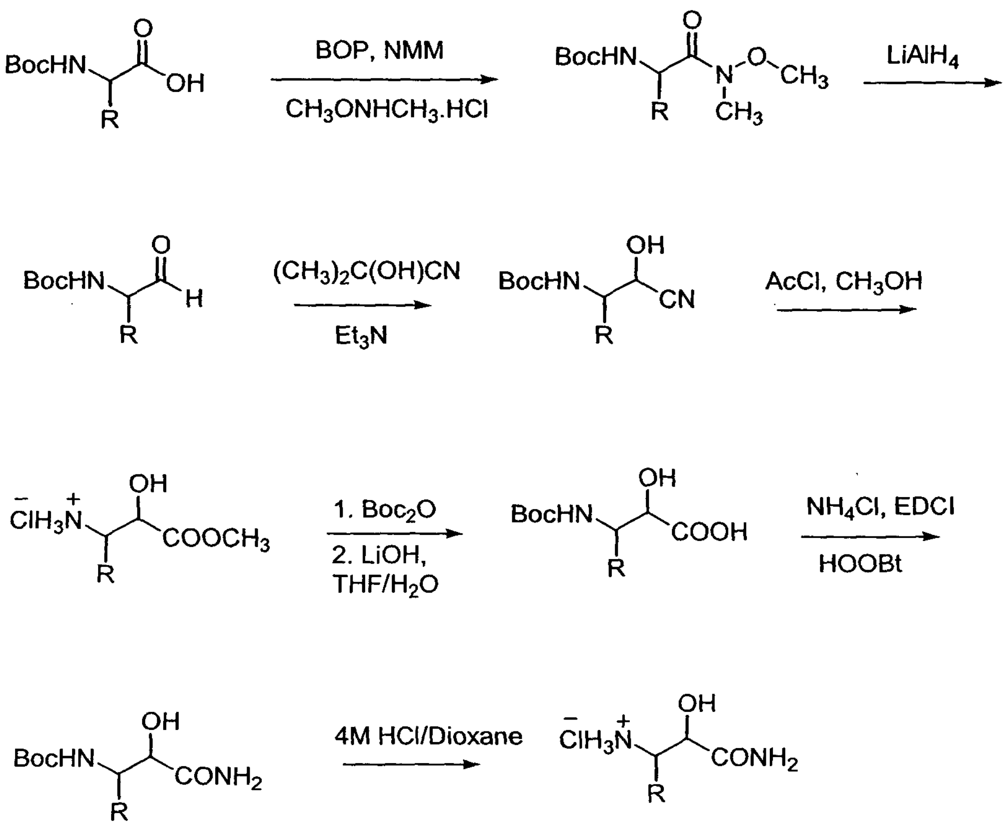
SCHEME 6



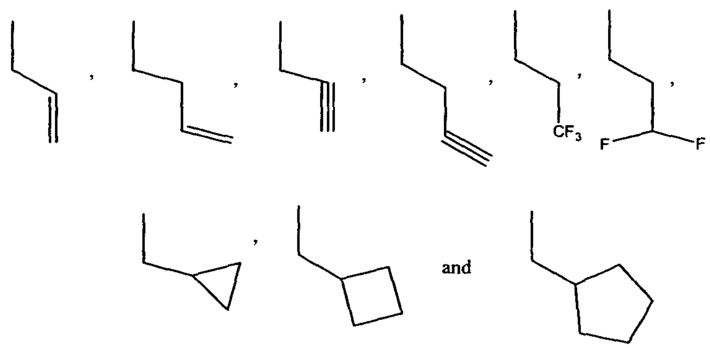
SCHEME 7


HCl
H_2N
OH
Ph
$CONMe_2$
Iboc·Chg
(7.1)
(2.3)
HOOBt
EDCI
NMM
(7.2)
Moffatt oxidation
(7.3)
SH SH
$BF_3 \cdot Et_2O$
(7.4)

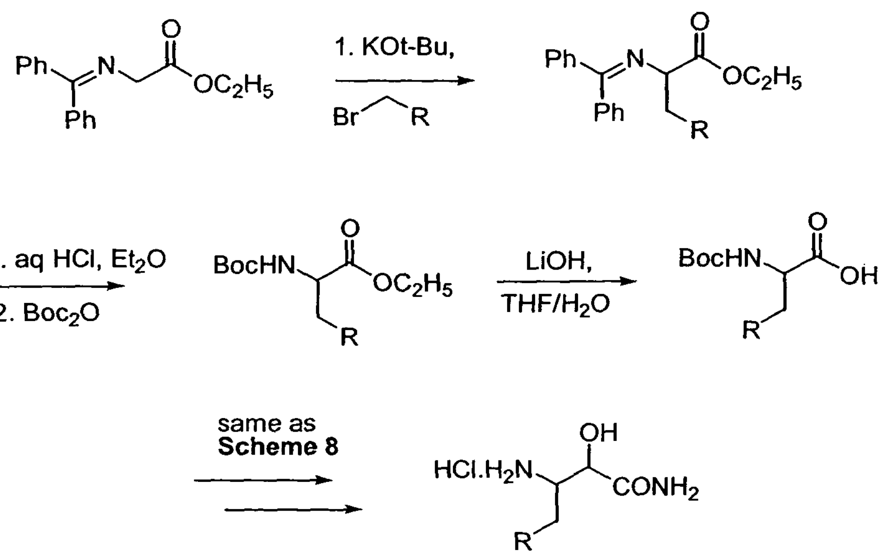
SCHEME 8



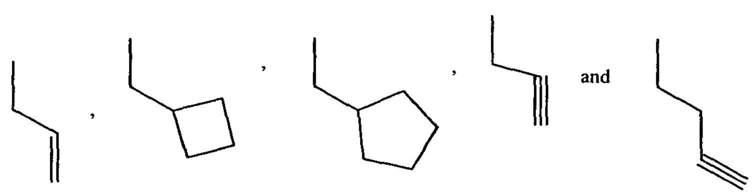
where R =



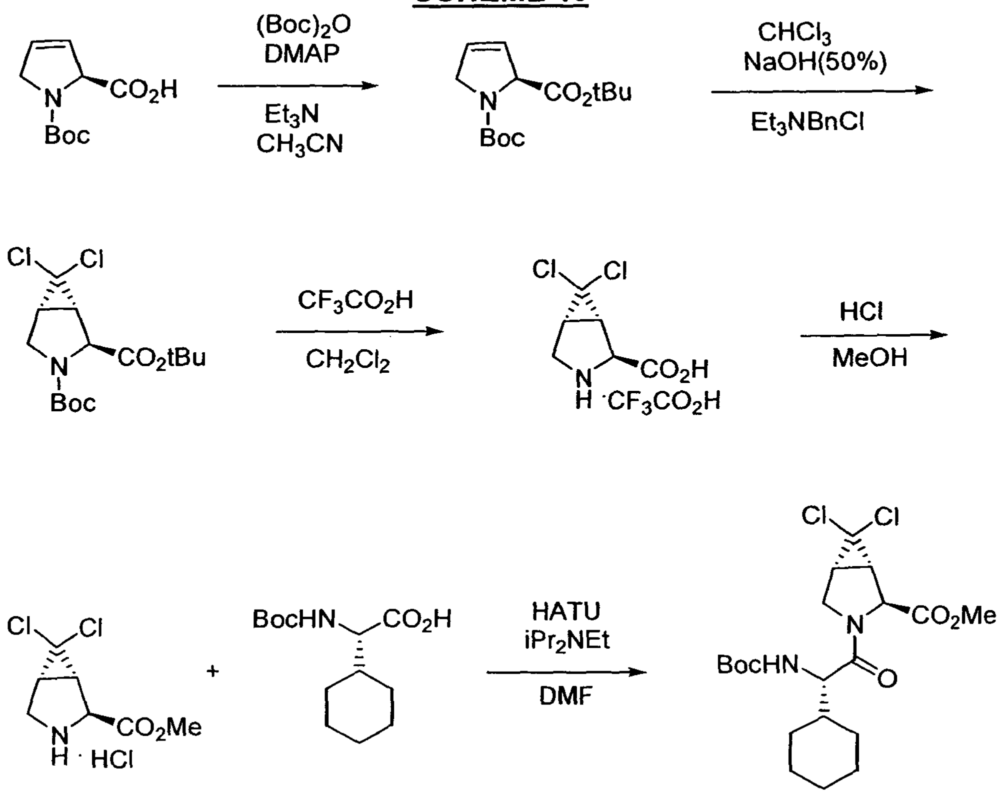
SCHEME 9



where R =

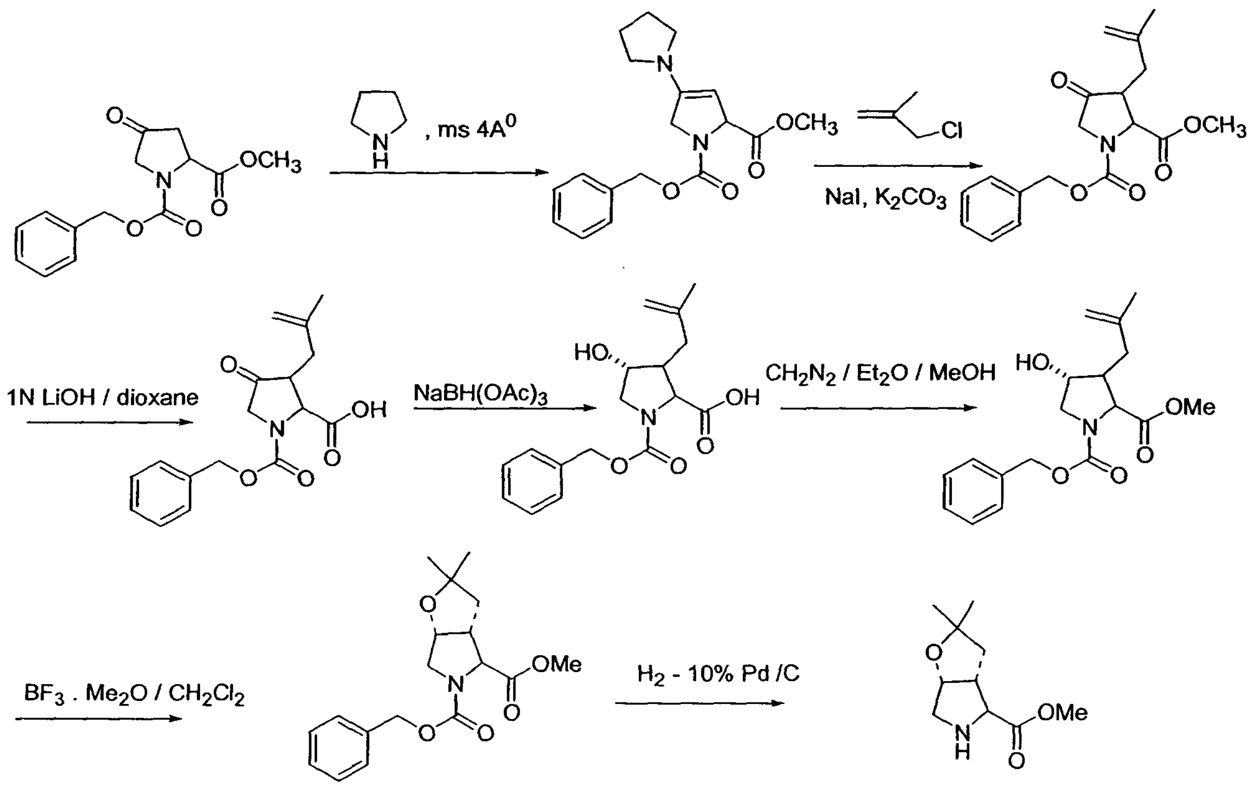


SCHEME 10

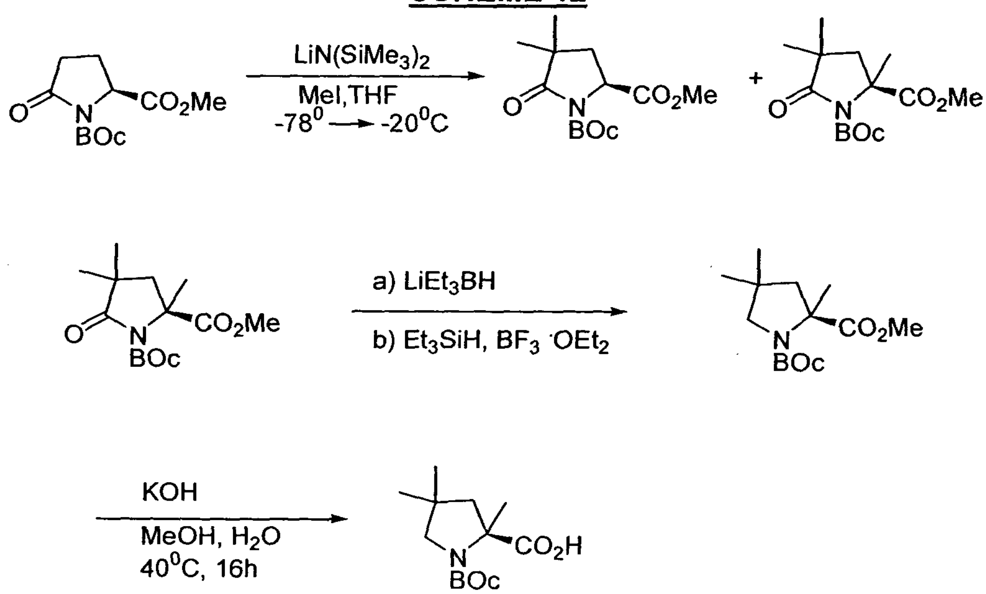


(Boc)2O
DMAP
Et3N
CH3CN
CO2H
Boc
CO2tBu
CHCl3
NaOH(50%)
Et3NBnCl
Cl
CF3CO2H
CH2Cl2
H ·CF3CO2H
HCl
MeOH
CO2Me
H · HCl
BocHN
HATU
iPr2NEt
DMF

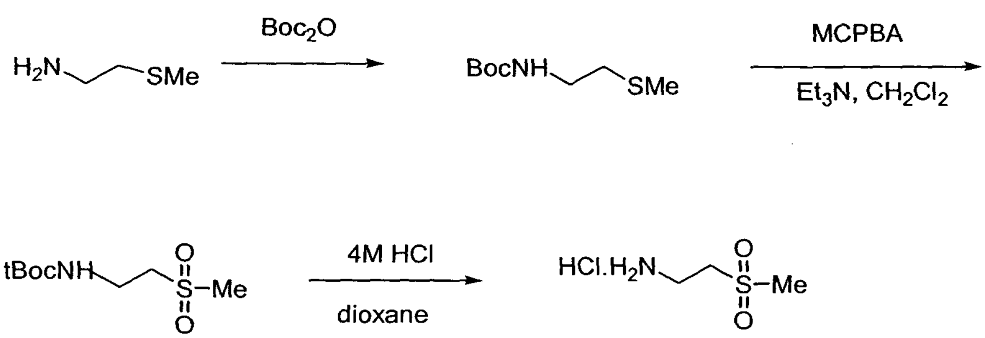
SCHEME 11


, ms 4A0
NaI, K2CO3
1N LiOH / dioxane
NaBH(OAc)3
CH2N2 / Et2O / MeOH
BF3 . Me2O / CH2Cl2
H2 - 10% Pd /C

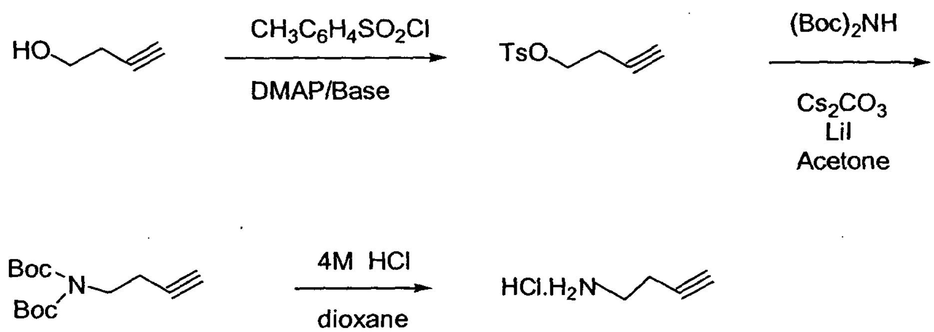
SCHEME 12



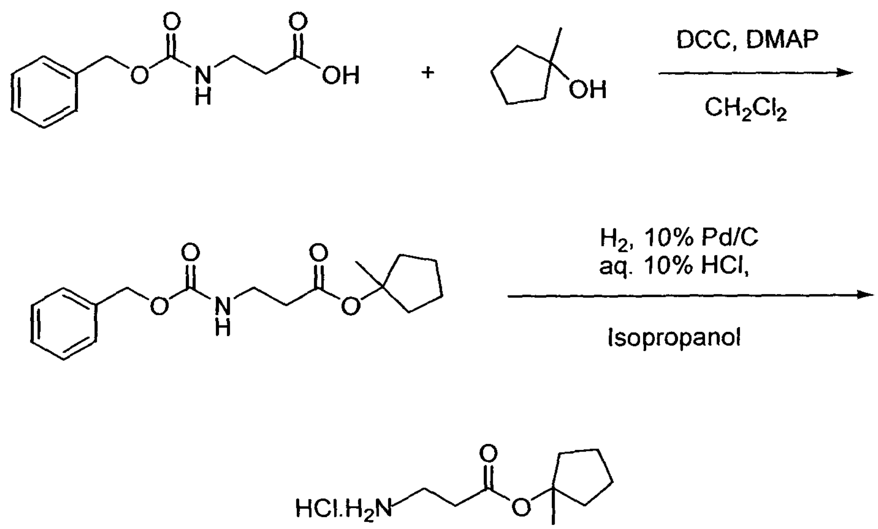
SCHEME 13



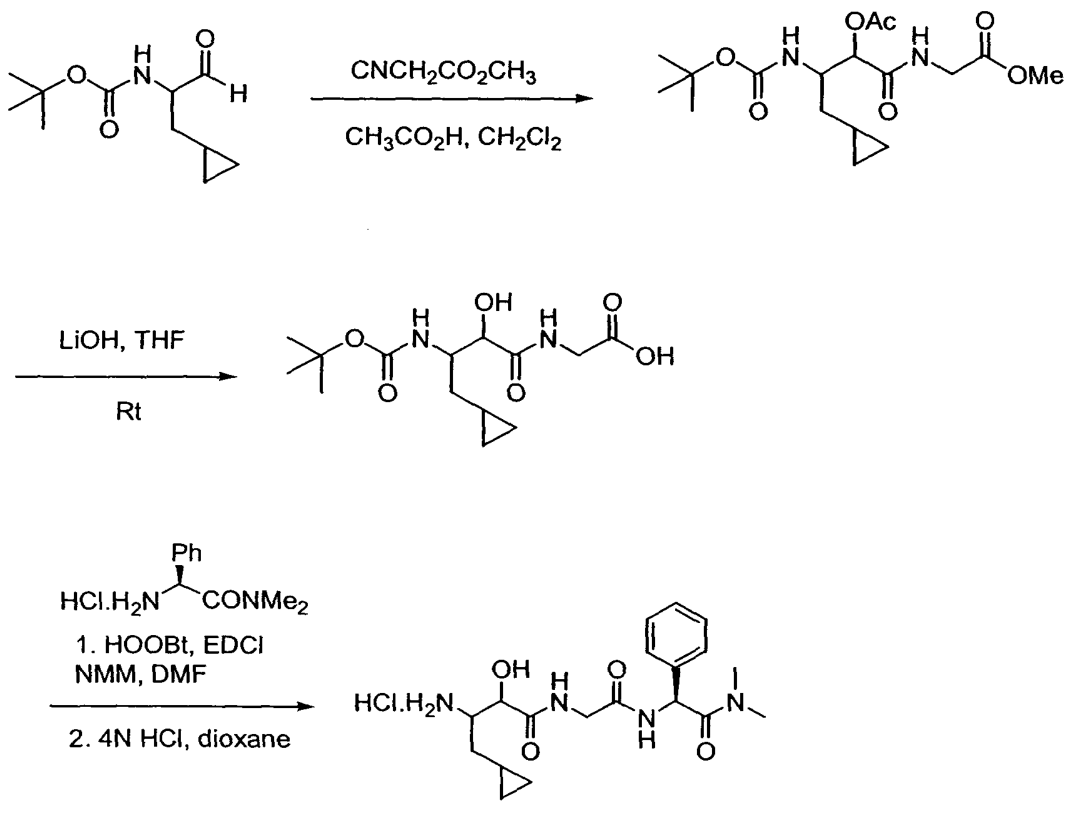
SCHEME 14



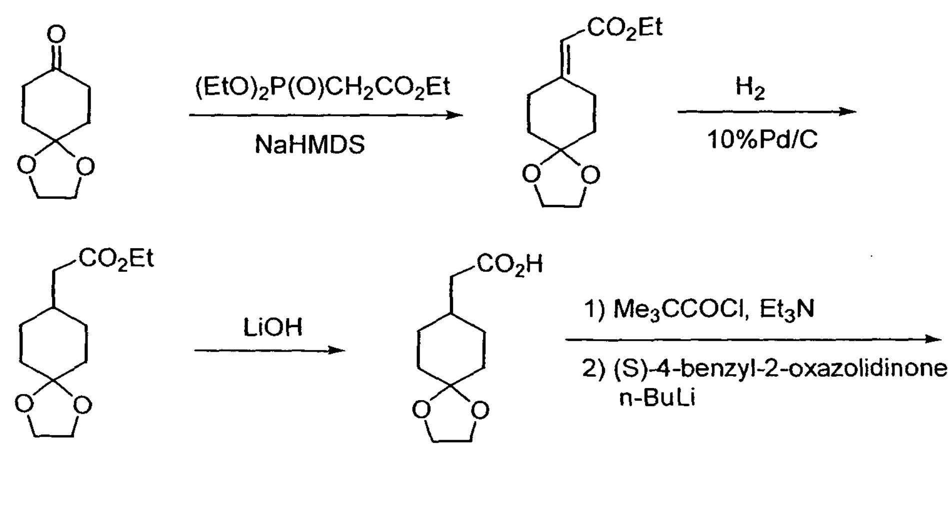
SCHEME 15

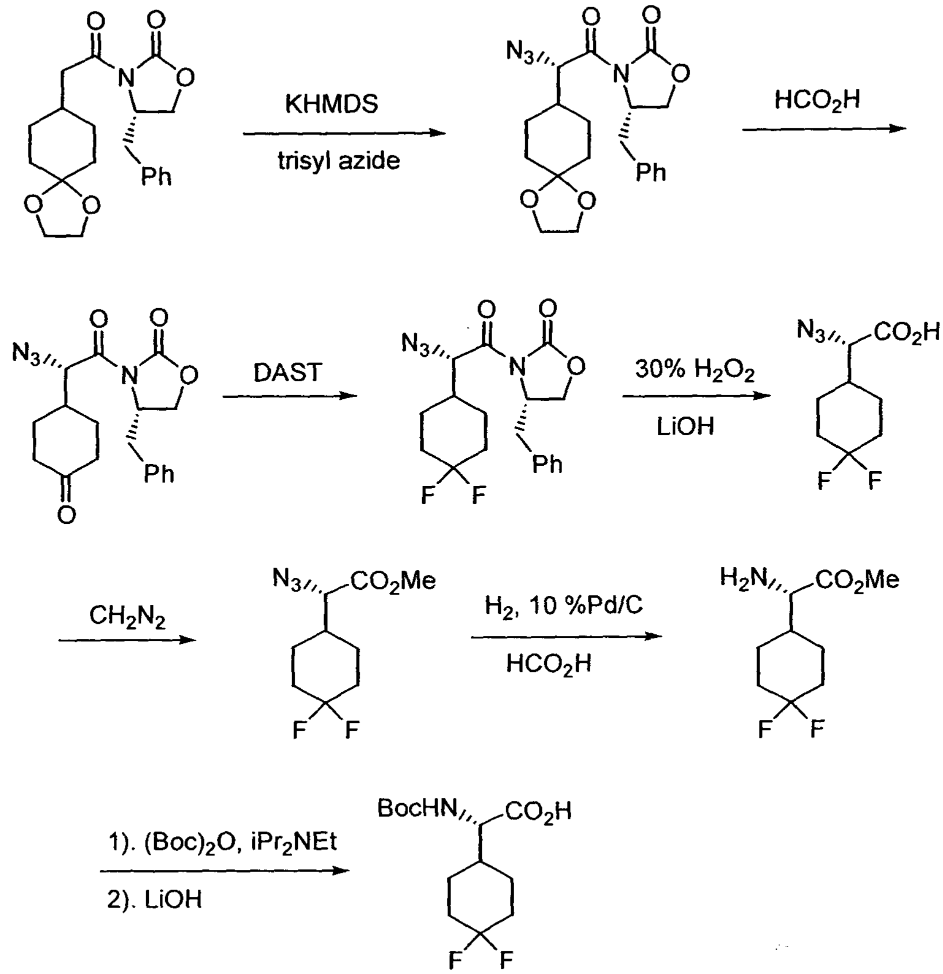


SCHEME 16

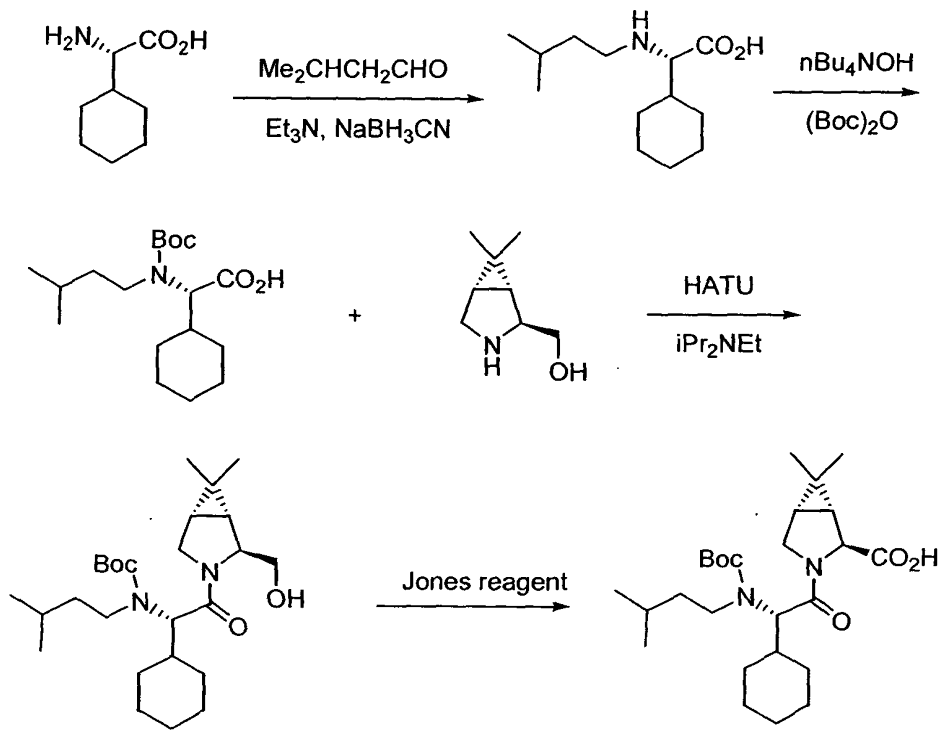


SCHEME 17

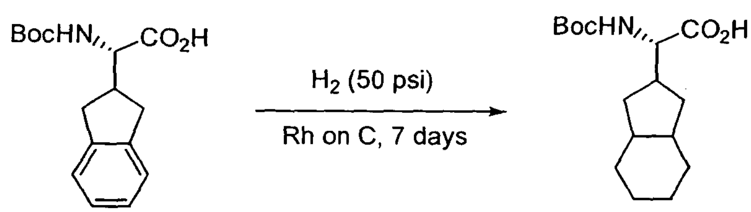



KHMDS
trisyl azide
HCO2H
DAST
30% H2O2
LiOH
CH2N2
H2, 10 %Pd/C
HCO2H
1). (Boc)2O, iPr2NEt
2). LiOH

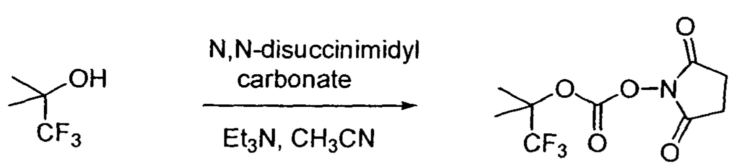
SCHEME 18



SCHEME 19



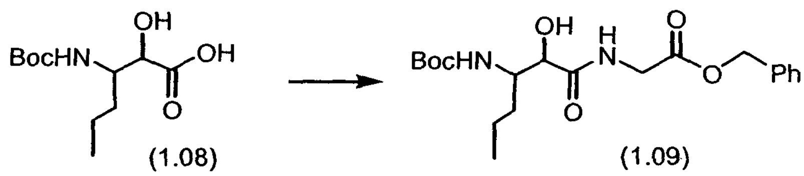
SCHEME 20



Preparation of Intermediates:

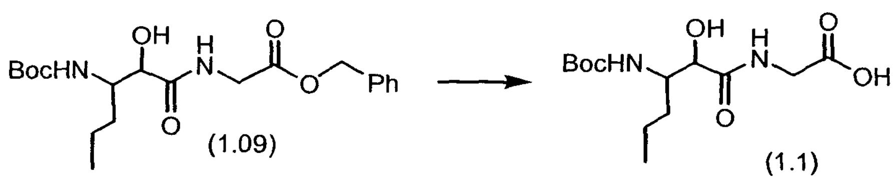
Preparative Example 1

Step A: Compound (1.1)



To a stirred solution of Compound (1.08)(3.00 g, 12.0 mmol (S. L. Harbeson *et al.* J.Med.Chem. 37 No.18 (1994) 2918-2929) in DMF (15 mL) and CH_2Cl_2 (15 mL) at -20°C was added HOOBt (1.97 g, 12.0 mmol), *N*-methyl morpholine (4.0 mL, 36.0 mmol) and EDCI (2.79 g, 14.5 mmol) and stirred for 10 minutes, followed by addition of HCl·H_2N-Gly-OBn (2.56 g, 13.0 mmol). The resulting solution was stirred at -20°C for 2 hrs, kept refrigerated overnight and then concentrated to dryness, followed by dilution with EtOAc (150 mL). The EtOAc solution was then washed twice with saturated $NaHCO_3$, H_2O, 5% H_3PO_4, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the Compound (1.09) (4.5 g, 94%). LRMS *m/z* MH^+= 395.1.

Step B: Compound (1.1)

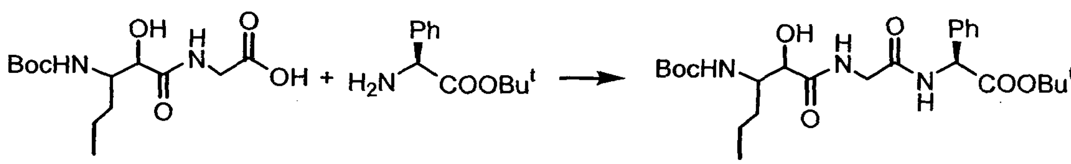


A solution of Compound (1.09) (7.00 g, 17.8 mmol) in absolute ethanol (300 mL) was stirred at room temperature under a hydrogen atmosphere in the presence of Pd-C (300 mg, 10%). The reaction progress was monitored by tlc. After 2 h, the mixture was filtered through a celite pad and the resulting solution

was concentrated in vacuo to give Compound (1.1) (5.40 g, quantitative). LRMS *m/z* MH^+= 305.1.

Preparative Example 2

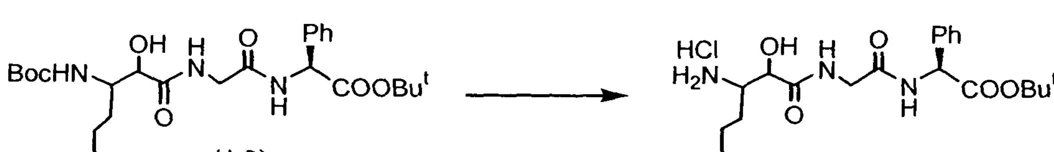
Step A Compound (1.3)



(1.1) (1.2) (1.3)

A mixture of Compound (1.1) from Preparative Example 1, Step B above (1 eq.), Compound (1.2) (from Novabiochem, Catalog No. 04-12-5147) (1.03 eq.), HOOBt (1.03 eq.), N-methylmorpholine (2.2 eq.), and dimethylformamide (70 mL/g) was stirred at -20°C. EDCI (1.04 eq.) was added and the reaction stirred for 48 hr. The reaction mixture was poured into 5% aqueous KH_2PO_4 and extracted with ethyl acetate (2 x). The combined organics were washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine, and the organic layer was dried over anhydrous $MgSO_4$. The mixture was filtered, then evaporated and the filtrate dried under vacuum, the residue was triturated with Et_2O-hexane, and filtered to leave the title compound (1.3)(86% yield), $C_{25}H_{39}N_3O_7$ (493.60), mass spec. (FAB) M+1 = 494.3.

Step B Compound (1.4)

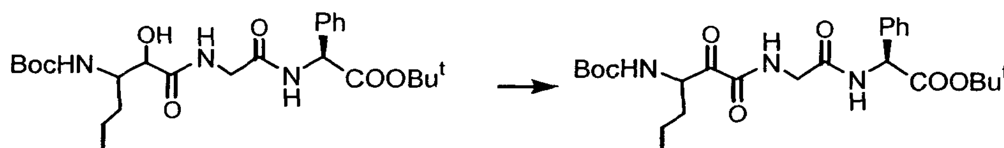


(1.3) (1.4)

Compound (1.3) from Preparative Example 2, Step A (3.0 g) was treated with 4 N HCl/dioxane (36 mL) and stirred at room temperature for 7 min. The mixture was poured into 1.5 L cold (5°C) hexane and stirred, then allowed to set cold for 0.5 hr. The mixture was suction-filtered in a dry atmosphere, and the collected solid was further dried to afford the title compound (1.4) (2.3 g, 88% yield), $C_{20}H_{31}N_3O_5{\cdot}HCl$, H^1 NMR (DMSO-d6/NaOD) δ 7.38 (m, 5H), 5.25 (m, 1H), 4.3-4.1 (m, 1H), 3.8 (m, 2H), 3.4-3.3 (m, obscured by D_2O), 1.7-1.1 (m, 4H), 1.35 (s, 9H), 0.83 (m, 3H).

Preparative Example 3

Compound (1.5)

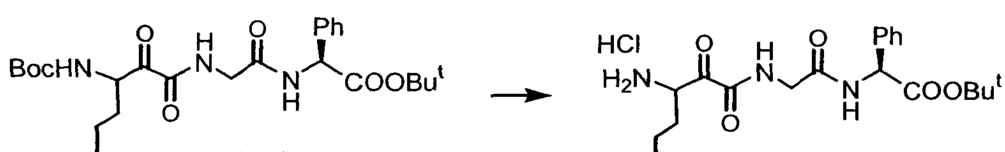


(1.3) (1.5)

Compound (1.3) from Preparative Example 2, Step A, was treated in essentially the same manner as in Preparative Example 7, Step A below to afford Compound (1.5).

Preparative Example 4

Compound (1.6)

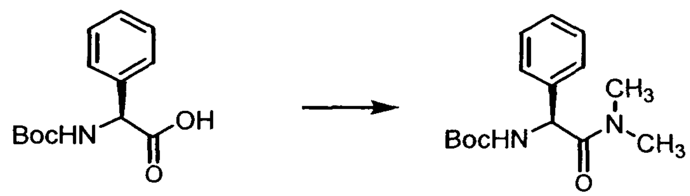


(1.5) (1.6)

Compound (1.5) from Preparative Example 3, was treated in essentially the same manner as in Preparative Example 2, Step B, to afford Compound (1.6).

Preparative Example 5

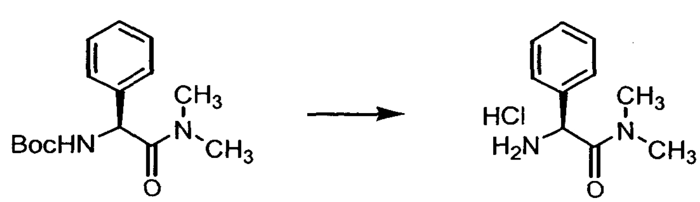
Step A Compound (2.09)



(2.08) (2.09)

To a solution of dimethylamine hydrochloride (1.61 g, 19.7 mmol), *N*-Boc-phenylglycine, Compound (2.08)(4.50 g, 17.9 mmol, Bachem Co. # A-2225), HOOBt (3.07 g, 18.8 mmol) and EDCl (4.12 g, 21.5 mmol) in anhydrous DMF (200 mL) and CH_2Cl_2 (150 mL) at -20°C was added NMM (5.90 mL, 53.7 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then allowed to warm to rt, and EtOAc (450 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. After the layers were separated, the organic layer was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford Compound (2.09) (4.86 g) as a white solid, which was used without further purification.

Step B Compound (2.1)

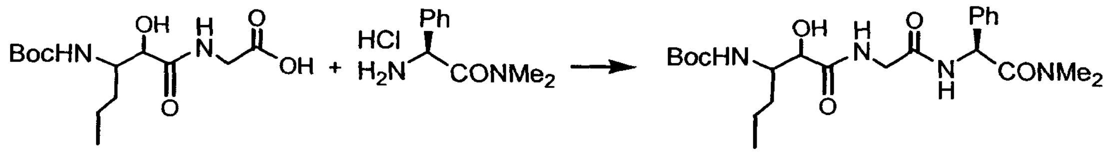


(2.09) (2.1)

Compound (2.09) from Preparative Example 5, Step A (4.70 g, crude) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo to yield Compound (2.1) as a white solid which was used in the next reaction without further purification. LRMS *m/z* MH^+= 179.0.

Preparative Example 6

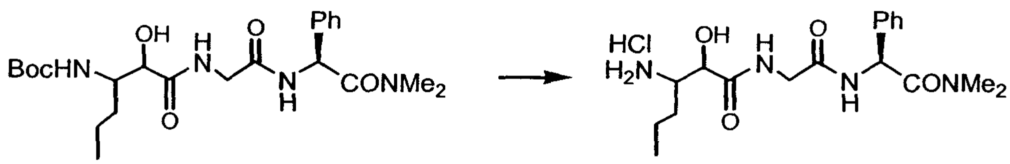
Step A Compound (2.2)



(1.1) (2.1) (2.2)

In essentially the same manner as Preparative Example 2, Step A. substituting phenylglycine N,N-dimethylamide hydrochloride in place of phenylglycine *t*-butyl ester hydrochloride, Compound (2.2) was prepared mass spec. (FAB) M+1 = 465.3.

Step B Compound (2.3)

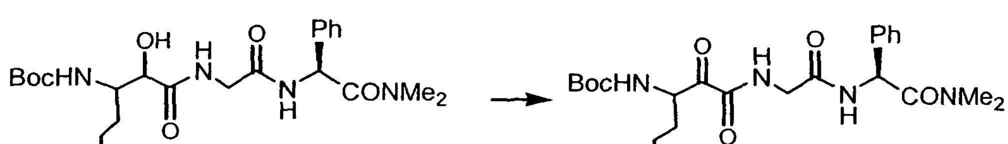


(2.2) (2.3)

Compound (2.2) from Step A (1.85 g) was reacted with 4 N HCl/dioxane (50 mL) at room temperature for 1 hr. The mixture was evaporated under vacuum in a 20°C water bath, triturated under isopropyl ether, filtered, and dried to afford Compound (2.3) (1.57 g, 98% yield), $C_{18}H_{28}N_4O_4 \cdot HCl$, mass spec. (FAB) M+1 = 365.3

Preparative Example 7

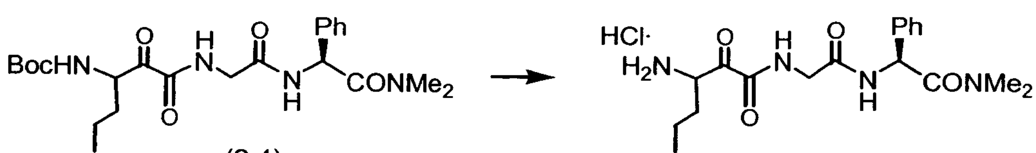
Step A Compound (2.4)



(2.2) (2.4)

A solution of Compound (2.2) from Preparative Example 5, Step A (2.0 g) in dichloromethane (60 mL) was treated with dimethylsulfoxide (3.0 mL) and 2,2-dichloroacetic acid (0.70 mL). The stirred mixture was cooled to 5°C and then added 1 M dicyclohexylcarbodiimide/ dichloromethane solution (8.5 mL). The cold bath was removed and the mixture stirred for 22 hr. Then added 2-propanol (0.5 mL), and stirred for an additional 1 hr. The mixture was filtered then washed with ice-cold 0.1 N NaOH (50mL), then ice-cold 0.1 N HCl (50 mL), then 5% aqueous KH_2PO_4, then saturated brine. The organic solution was dried over anhydrous magnesium sulfate, then filtered. The filtrate was evaporated, and chromatographed on silica gel, eluting with ethyl acetate to afford Compound (2.3) (1.87 g, 94% yield), $C_{23}H_{34}N_4O_6$, mass spec. (FAB) M+1 = 463.3.

Step B   Compound (2.5)

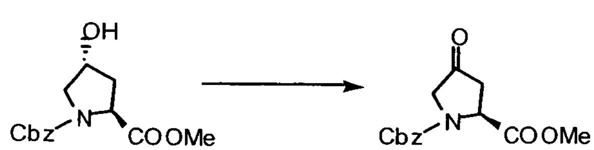


(2.4)   (2.5)

In essentially the same manner as Preparative Example 2, Step B, Compound (2.5) was prepared.

Preparative Example 8

Step A   Compound (3.1)

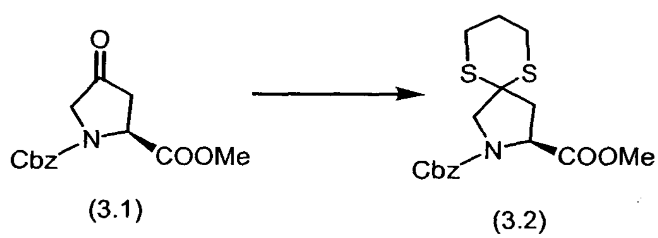


(3.01)   (3.1)

In a flask were combined N-Cbz-hydroxyproline methyl ester (available from Bachem Biosciences, Incorporated, King of Prussia, Pennsylvania), compound

(3.01) (3.0 g), toluene (30 mL), and ethyl acetate (30 mL). The mixture was stirred vigorously, and then a solution of NaBr/water (1.28 g /5 mL) was added. To this was added 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO, 17 mg, from Aldrich Chemicals, Milwaukee, Wisconsin). The stirred mixture was cooled to 5°C and then was added a prepared solution of oxidant [commercially available bleach, Clorox® (18 mL), $NaHCO_3$ (2.75 g) and water to make up 40 mL] dropwise over 0.5 hr. To this was added 2-propanol (0.2 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The organic extracts were combined, washed with 2% sodium thiosulfate, then saturated brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated the filtrate under vacuum to leave a pale yellow gum suitable for subsequent reactions (2.9 g, 97% yield), $C_{14}H_{15}NO_5$ (277.28), mass spec. (FAB) M+1 = 278.1.

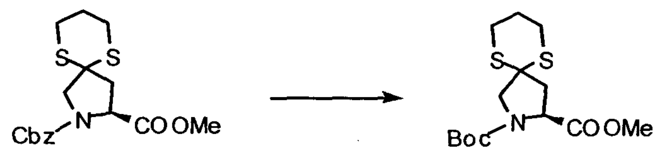
Step B   Compound (3.2).



Compound (3.1) from Step A above (7.8 g) was dissolved in dichloromethane (100 mL), and cooled to 15°C. To this mixture was first added 1,3-propanedithiol (3.1 mL), followed by freshly distilled boron trifluoride etherate (3.7 mL). The mixture was stirred at room temperature for 18 h. While stirring vigorously, a solution of K_2CO_3/water (2 g / 30 mL)was carefully added, followed by saturated $NaHCO_3$ (10 mL). The organic layer was separated from the aqueous layer (pH ~7.4), washed with water (10 mL), then brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with toluene,

then a with a gradient of hexane-Et_2O (2:3 to 0:1) to afford a brown oil (7.0 g, 68% yield), $C_{17}H_{21}NO_4S_2$ (367.48), mass spec. (FAB) M+1 =368.1.

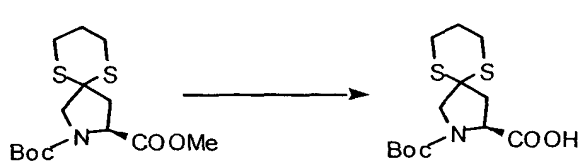
Step C Compound (3.3)



(3.2) (3.3)

A solution of compound (3.2) from Step B above (45 g) in acetonitrile (800 mL) at 20°C was treated with freshly distilled iodotrimethylsilane (53 mL) at once. The reaction was stirred for 30 min., then poured into a freshly prepared solution of di-t-butyldicarbonate (107 g), ethyl ether (150 mL), and diisopropylethylamine (66.5 mL). The mixture stirred for 30 min. more then was washed with hexane (2 x 500 mL). Ethyl acetate (1000 mL) was added to the lower acetonitrile layer, and then the layer was washed with 10% aqueous KH_2PO_4 (2 x 700 mL), and brine. The filtrate was evaporated under vacuum in a 25°C water bath, taken up in fresh ethyl acetate (1000 mL), and washed successively with 0.1 N HCl, 0.1 N NaOH, 10% aqueous KH_2PO_4, and brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue (66 g) was chromatographed on silica gel (2 kg), eluting with hexane (2 L), then Et_2O/hexane (55:45, 2 L), then Et_2O (2 L) to afford an orange gum which slowly crystallized on standing (28 g, 69% yield), $C_{14}H_{23}NO_4S_2$ (333.46), mass spec. (FAB) M+1 = 334.1.

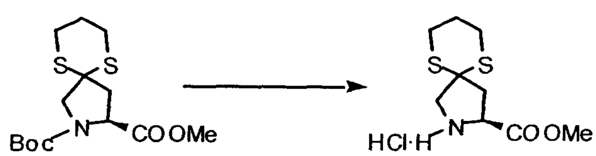
Step D Compound (3.4)



(3.3) (3.4)

A solution of compound (3.3) from Step C above (11 g) in dioxane (150 mL) at 20°C was treated with 1N aqueous LiOH (47 mL) and stirred for 30 h. The mixture was concentrated under vacuum in a 30°C water bath to half volume. The remainder was diluted with water (300 mL), extracted with Et_2O (2 x 200 mL). The aqueous layer was acidified to pH ~4 with 12 N HCl (3-4 mL), extracted with ethyl acetate, and washed with brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum to leave Compound (3.4) (8.1 g, 78%), $C_{13}H_{21}NO_4S_2$ (319.44), mass spec. (FAB) M+1 = 320.1.

Step E   Compound (3.5).

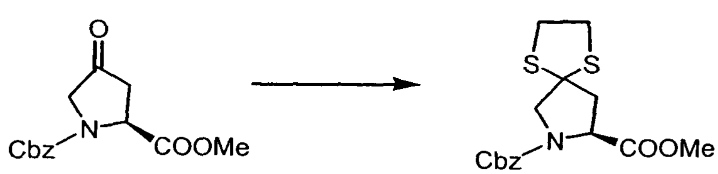


(3.3)   (3.5)

To a solution of compound (3.3) from Step C above (1 g) in dioxane (5 mL), was added 4 N HCl-dioxane solution (50 mL). The mixture was stirred vigorously for 1 hr. The mixture was evaporated under vacuum in a 25°C water bath. The residue was triturated with Et_2O, and filtered to leave the title compound (0.76 g, 93% yield), $C_9H_{15}NO_2S_2 \cdot HCl$ (269.81), mass spec. (FAB) M+1 = 234.0.

Preparative Example 9

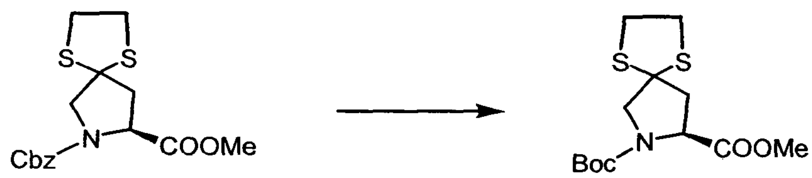
Step A   Compound (3.6)



(3.1)   (3.6)

Following essentially the same procedure of Preparative Example 8, Step B, substituting ethane dithiol for propane dithiol, compound (3.6) was obtained.

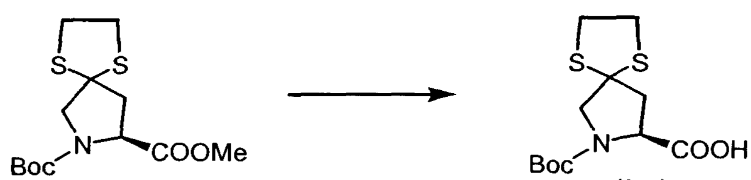
Step B Compound (3.7).



(3.6) (3.7)

Following essentially the same procedure of Preparative Example 8, Step C, substituting compound (3.6) for compound (3.2), the product compound (3.7) was obtained.

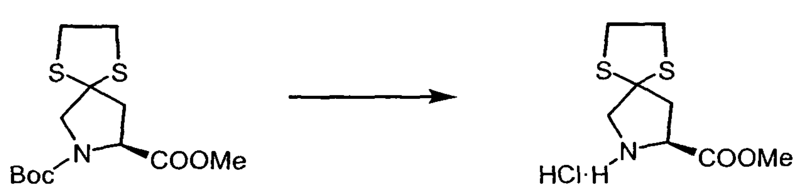
Step C Compound (3.8)



(3.7) (3.8)

Following essentially the same procedure of Preparative Example 8, Step D, substituting compound (3.7) for compound (3.3) the product compound (3.8) was obtained.

Step D Compound (3.9)

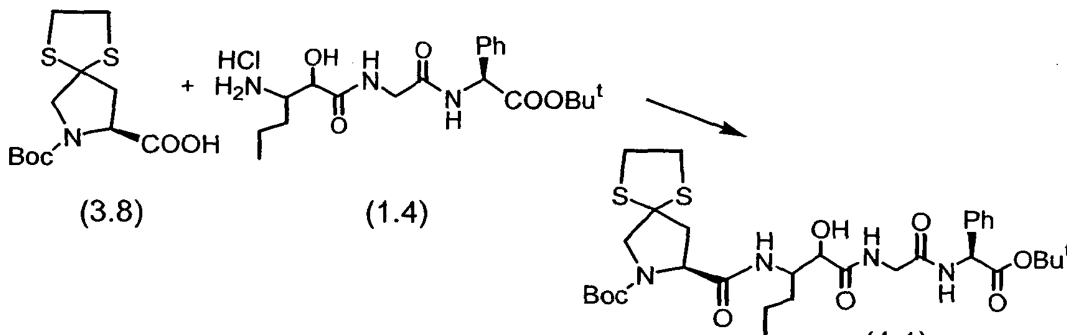


(3.7) (3.9)

Following essentially the same procedure of Preparative Example 8, Step E, substituting compound (3.7) for compound (3.3) the product compound (3.9) was obtained.

Preparative Example 10

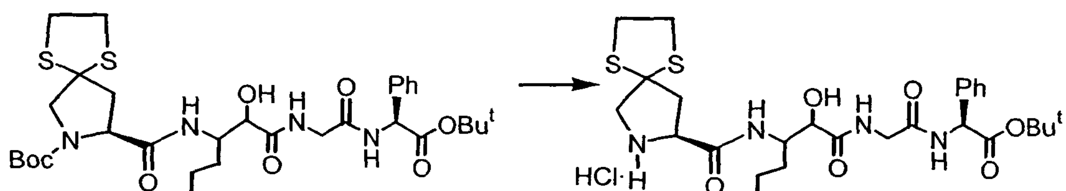
Step A Compound (4.1)



(3.8) (1.4) (4.1)

In essentially the same manner as Preparative Example 2, Step A, Compound (4.1) was prepared $C_{33}H_{48}N_4O_9S_2$ (708.89).

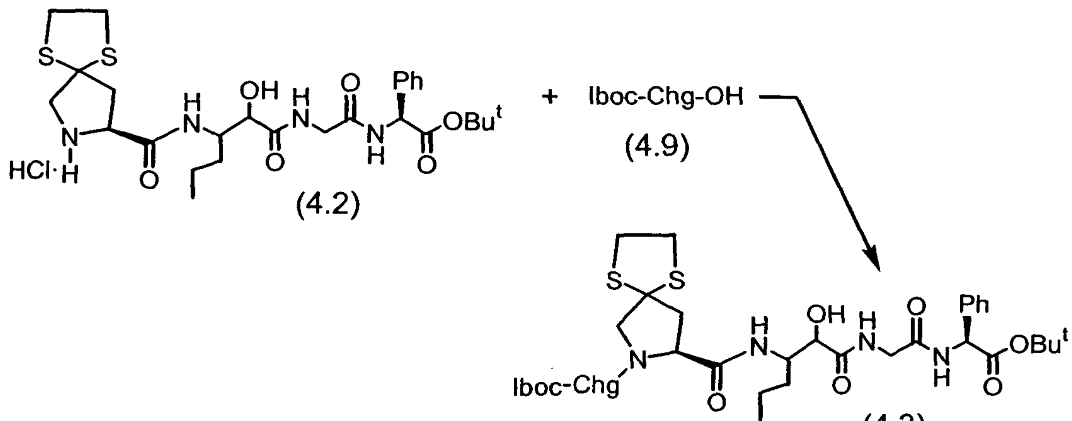
Step B Compound (4.2)



(4.1) (4.2)

In essentially the same manner as Preparative Example 2, Step B, Compound (4.2) was prepared mass spec. (FAB) M+1 = 609.3.

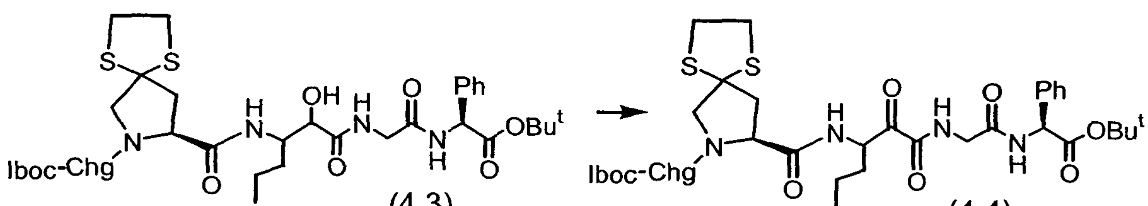
Step C Compound (4.3)



(4.2) (4.3)

In essentially the same manner as Preparative Example 2, Step A, Compound (4.3) was prepared, $C_{41}H_{61}N_5O_{10}S_2$ (708.89), mass spec. (FAB) M+1 = 709.3.

Step D Compound (4.4)

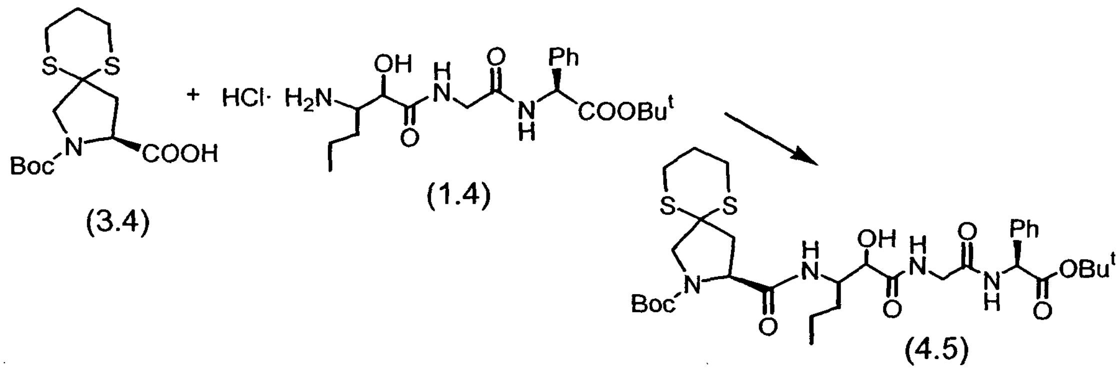


(4.3) (4.4)

In essentially the same manner as Preparative Example 7, Step A, Compound (4.4) was prepared.

Preparative Example 11

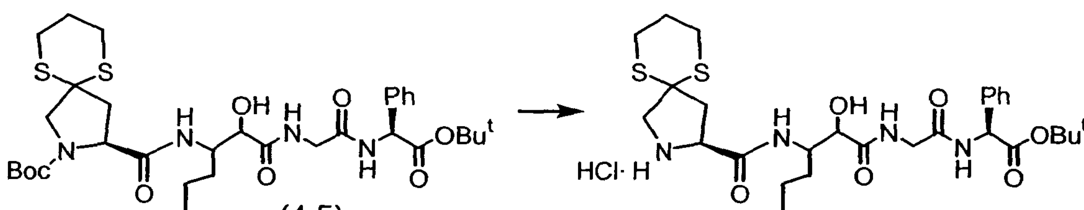
Step A Compound (4.5)



(3.4) (1.4) (4.5)

In essentially the same manner as Preparative Example 2, Step A, Compound (4.5) was prepared.

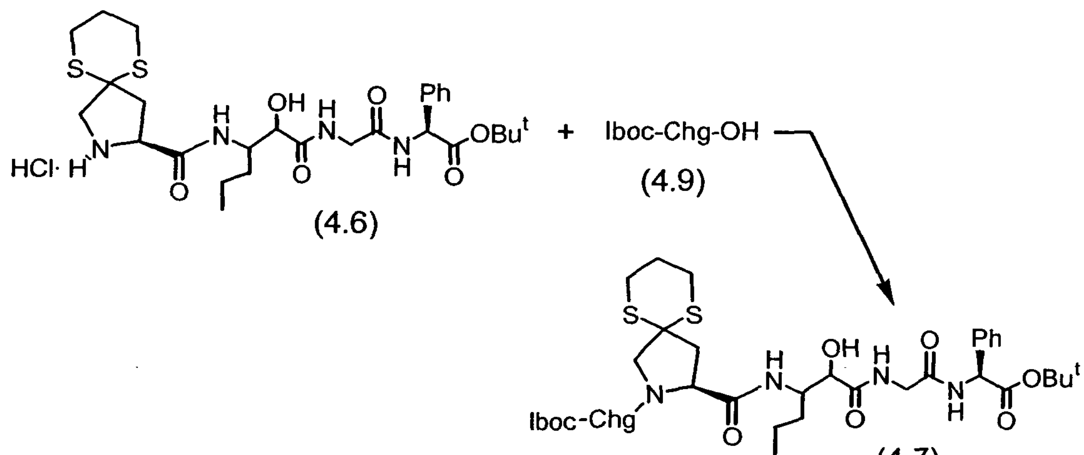
Step B, Compound (4.6)



(4.5) (4.6)

In essentially the same manner as Preparative Example 2, Step B, Compound (4.6) was prepared.

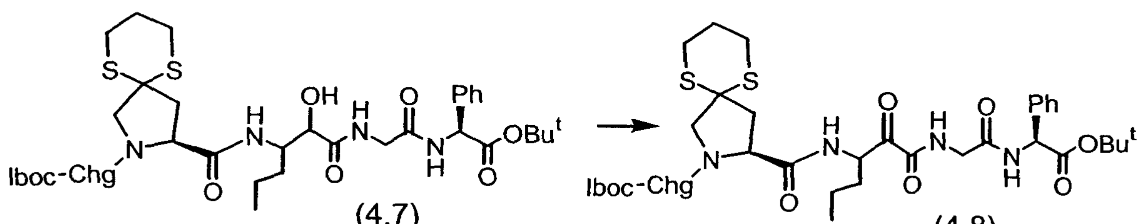
Step C, Compound (4.7)



(4.6) (4.9) (4.7)

Compound (4.9) from Preparative Example 12, was reacted with Compound (4.6) from Step B above, in essentially the same manner as Preparative Example 2, Step A, to afford Compound (4.7).

Step D, Compound (4.8)



(4.7) (4.8)

In essentially the same manner as Preparative Example 7, Step A, Compound (4.8) was prepared.

Preparative Example 12

Compound (4.9)

i-BuOCOCl + H-Chg-OH ⟶ Iboc-Chg-OH

(4.01) (4.02) (4.9)

A solution of L-cyclohexylglycine (4.02) (1.0 eq.), dimethylformamide (20 mL/g), and diisopropylethylamine (1.1 eq.) at 5°C is treated with isobutyl chloroformate (4.01) (1.1 eq.). The cold bath is removed and it is stirred for 6 hr.

The reaction mixture is poured into 5% aqueous KH_2PO_4 and extracted with ethyl acetate (2 x). The combined organics are washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine, and the organics are dried over anhydrous $MgSO_4$. The mixture is filtered, the filtrate evaporated under vacuum, the residue chromatographed if necessary or else the residue triturated with Et_2O-hexane, and filtered to leave the title compound (4.9), $C_{13}H_{23}NO_4$ (257.33).

Preparative Example 13

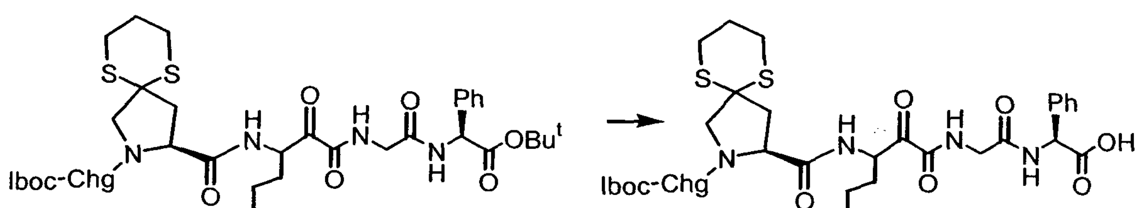
Compound (13.1)

i-BuOCOCl + H-Thr(Bzl)-OH ⟶ Iboc-Thr(Bzl)-OH

(4.01) (13.02) (13.1)

In essentially the same manner as Preparative Example 12, substituting L-O-benzylthreonine (13.02) (Wang *et al*, *J. Chem. Soc., Perkin Trans.* 1, (1997) No. 5, 621-624.) for L-cyclohexylglycine (4.02) Compound (13.1) is prepared $C_{16}H_{23}NO_5$ (309.36), mass spec. (FAB) M+1 = 310.2.

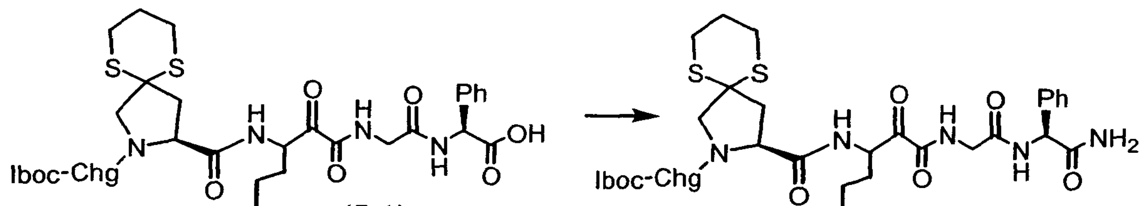
Preparative Example 14



(4.8) (5.1)

Compound (4.8) from Preparative Example 11, Step D (1.0 g) was reacted with a solution of anhydrous trifluoroacetic acid-dichloromethane (1:1, 50 mL) for 2 hr. The solution was diluted with xylene (100 mL) and evaporated under vacuum. The residue was triturated with Et_2O, and filtered to leave the title compound (5.1) (0.9 g), $C_{37}H_{53}N_5O_9S_2$ (775.98), mass spec. (FAB) M+1 =776.5.

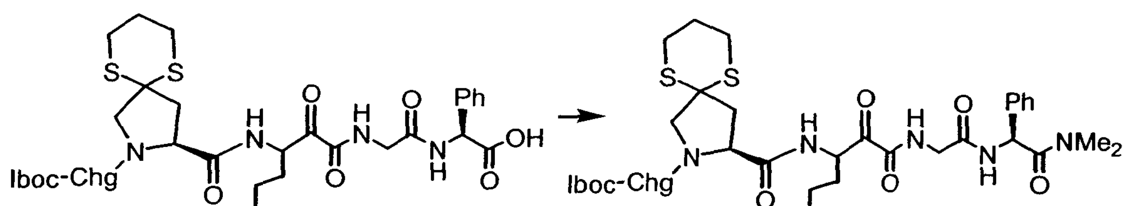
Step B Compound (5.2)



(5.1) (5.2)

In essentially the same manner as Preparative Example 2, Step A, Compound (5.1) was reacted with ammonia (0.5 M 1,4-dioxane solution), to obtain the title compound (5.2) $C_{37}H_{54}N_6O_8S_2$ (774.99), mass spec. (FAB) M+1 = 775.4.

Preparative Example 15

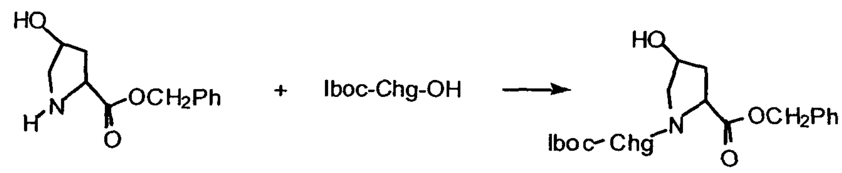


(5.1) (5.3)

A mixture of Compound (5.1) from Preparative Example 14, Step A (0.15 g), N,N-dimethylamine (0.12 mL of 2 M THF solution), dimethylformamide (10 mL), and PyBrOP coupling reagent (0.11 g) was cooled to 5°C, then diisopropylethylamine (DIEA or DIPEA, 0.12 mL) was added. The mixture was stirred cold for 1 min., then stirred at room temperature for 6 hr. The reaction mixture was poured into cold 5% aqueous H_3PO_4 (50 mL) and extracted with ethyl acetate (2 x). The combined organics were washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with MeOH-CH_2Cl_2 to afford the title compound (5.3), $C_{39}H_{58}N_6O_8S_2$ (803.05), mass spec. (FAB) M+1 =803.5.

Preparative Example 16

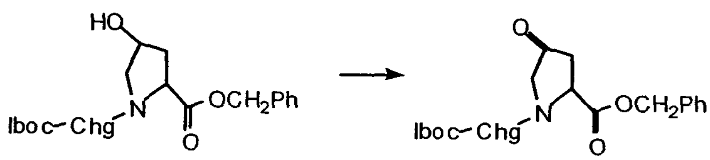
Step A Compound (6.2)



(6.1) 4.9) (6.2)

In essentially the same manner as Preparative Example 2, Step A, Compound (6.1) hydroxyproline benzyl ester hydrochloride was reacted with Compound (4.9) from Preparative Example 12, to obtain the title compound (6.2), $C_{25}H_{36}N_2O_6$ (460.56), mass spec. (FAB) M+1 = 461.2.

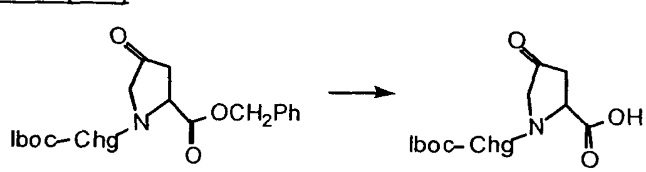
Step B Compound (6.3)



(6.2) (6.3)

In essentially the same manner as Preparative Example 8, Compound (6.3) was prepared, $C_{25}H_{34}N_2O_6$ (458.55), mass spec. (FAB) M+1 = 459.2.

Step C Compound (6.4)



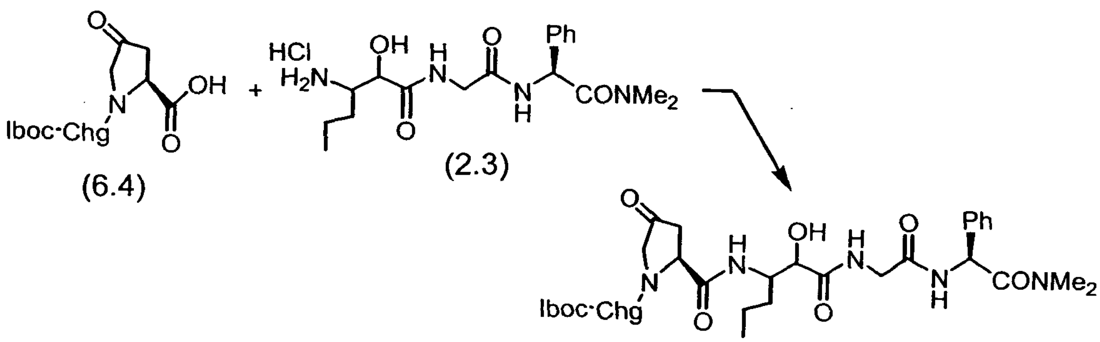
(6.3) (6.4)

A mixture of Compound (6.3) from Step B (1 g), 10% Pd/C (0.05 g), and EtOH (100 mL) was stirred under 1 atm. H_2 for 6 hr. The mixture was filtered, and

evaporated to dryness under vacuum to leave the title compound (6.4) (0.77 g), $C_{18}H_{28}N_2O_6$ (368.42) mass spec. (FAB) M+1 = 369.2.

Preparative Example 17

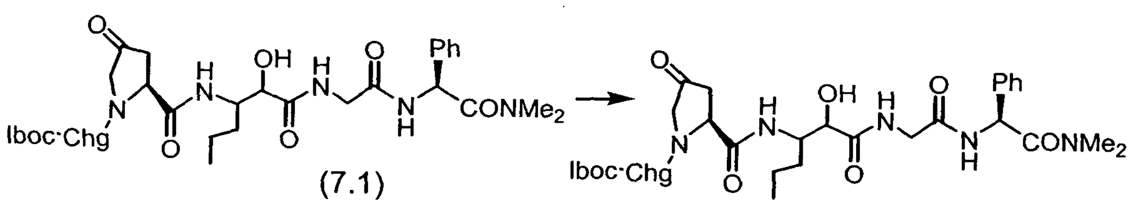
Step A Compound (7.1)



(6.4) (2.3) (7.1)

Compound (6.4) from Preparative Example 16, Step C, was reacted with Compound (2.3) from Preparative Example 6, Step B, in essentially the same manner as Preparative Example 2, Step A, to afford Compound (7.1), $C_{36}H_{54}N_6O_9$ (714.85), mass spec. (FAB) M+1 = 715.9.

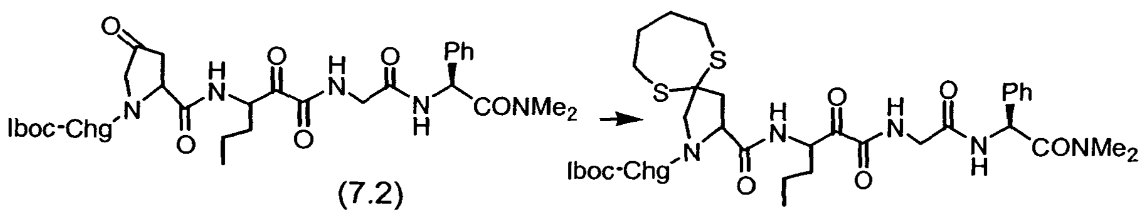
Step B Compound (7.2)



(7.1) (7.2)

Compound (7.1) was reacted in essentially the same manner as Preparative Example 7, Step A, to afford Compound (7.2), $C_{36}H_{52}N_6O_9$ (712.83), mass spec. (FAB) M+1 = 713.5.

Step C Compound (7.3)



(7.2) (7.3)

Compound (7.2) from Step B above, was reacted in essentially the same manner as Preparative Example 8, Step B, with 1,4-butanedithiol, to obtain the title compound (7.3), $C_{40}H_{60}N_6O_8S_2$ (817.07), mass spec. (FAB) M+1 = 817.5.

Using the above-noted and herein-described procedures, the compounds in the attached **Tables 2 through 6** were prepared. As a general note to all the Tables (1 through 6) that are attached hereto as well as to the Examples and Schemes in this specification, any open-ended nitrogen atom with unfulfilled valence in the chemical structures in the Examples and Tables refers to NH, or in the case of a terminal nitrogen, $-NH_2$. Similarly, any open-ended oxygen atom with unfulfilled valence in the chemical structures in the Examples and Tables refers to -OH and any open-ended carbon atom with unfilled valence is appropriately filled with -H.

Solid Phase Synthesis:

General procedure for solid-phase coupling reactions.

The synthesis was done in a reaction vessel which was constructed from a polypropylene syringe cartridge fitted with a polypropylene frit at the bottom. The Fmoc-protected amino acids were coupled under standard solid-phase techniques. Each reaction vessel was loaded with 100 mg of the starting Fmoc-Sieber resin (approximately 0.03 mmol). The resin was washed with 2 mL portions of DMF (2 times). The Fmoc protecting group was removed by treatment with 2 mL of a 20 % v/v solution of piperidine in DMF for 20 min. The resin was washed with 2 mL portions of DMF (4 times). The coupling was done in DMF (2 mL), using 0.1 mmol of Fmoc-amino acid, 0.1 mmol of HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and 0.2 mmol of DIPEA (N,N-diisopropylethylamine). After shaking for 2 h, the reaction

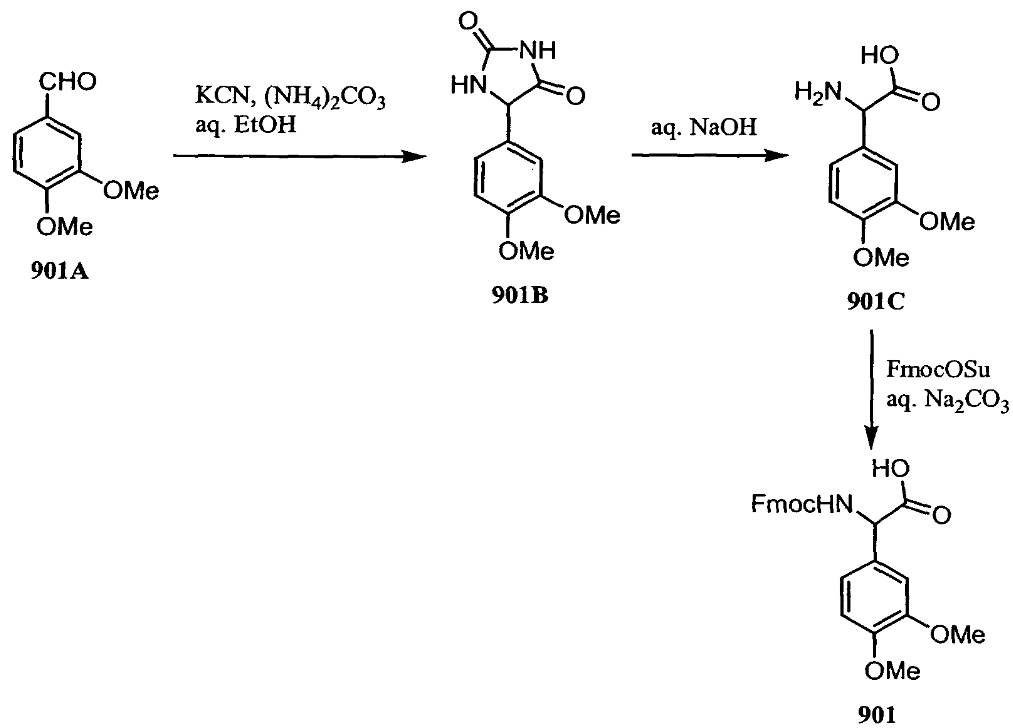
vessel was drained and the resin was washed with 2 mL portions of DMF (4 times). The coupling cycle was repeated with the next Fmoc-amino acid or capping group.

General procedure for solid-phase Dess-Martin oxidation.

The synthesis was conducted in a reaction vessel which was constructed from a polypropylene syringe cartridge fitted with a polypropylene frit at the bottom. Resin–bound hydroxy compound (approximately 0.03 mmol) was treated with a solution of 0.12 mmol of Dess-Martin periodinane and 0.12 mmol of t-BuOH in 2 mL of DCM for 4 h. The resin was washed with 2 mL portions of a 20 % v/v solution of iPrOH in DCM, THF, a 50 % v/v solution of THF in water (4 times), THF (4 times) and DCM (4 times).

Preparative Example 18

Preparation of N-Fmoc-2',3'-dimethoxyphenylglycine Compound (901)

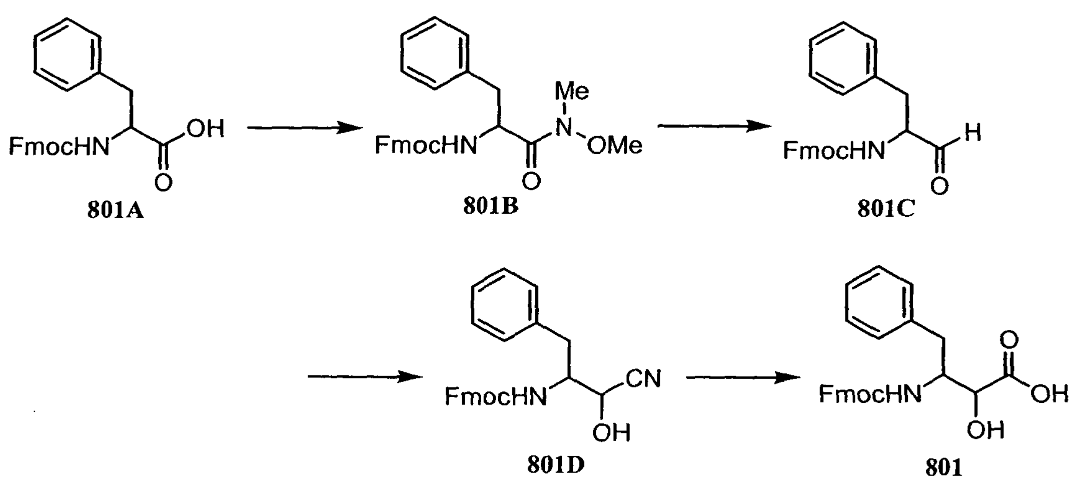


To a solution of potassium cyanide (1.465 g, 22.5 mmol) and ammonium carbonate (5.045 g, 52.5 mmol) in water (15 mL) was added a solution of 2,3-dimethoxybenzaldehye **901A** (2.5 g, 15 mmol) in ethanol (15 mL). The reaction mixture was heated at 40 °C for 24 h. The volume of the solution was reduced to 10 mL by evaporating under reduced pressure. Concentrated hydrochloric acid (15 mL) was added and compound **901B** was obtained as a white precipitate. Compound **901B** was isolated by filtration (2.2 g, 9.3 mmol). Compound **901B** was dissolved in 10 % w/w aqueous sodium hydroxide solution (15 mL) and the resulting solution was heated under reflux for 24 h. Concentrated hydrochloric acid was added and the pH was adjusted to neutral (pH 7). The resulting solution containing compound **901C** was evaporated under reduced pressure. The residue was dissolved in 5 % w/w aqueous sodium bicarbonate solution (150 mL).

The solution was cooled to 0 °C in an ice bath and 1,4-dioxane (30 mL) and a solution of 9-fluorenylmethyl succinimidyl carbonate (2.7 g, 8 mmol) in 1,4-dioxane (30 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 24 h. 1,4-dioxane was evaporated under reduced pressure. The aqueous solution was washed with diethyl ether. Concentrated hydrochloric acid was added and the pH was adjusted to acidic (pH 1). Ethyl acetate was added the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the desired compound **901** as a white foamy solid (3.44 g, 7.9 mmol). MS (LCMS-Electrospray) 434.1 MH^+.

Preparative Example 19

Compound (801)



To a solution of N-Fmoc-phenylalanine **801A** (5 g, 12.9 mmol) in anhydrous DCM (22 mL) cooled to -30°C in a dry ice-acetone bath was added N-methylpyrrolidine (1.96 mL, 16.1 mmol) and methyl chloroformate (1.2 mL, 15.5 mmol) sequentially. The reaction mixture was stirred at -30°C for 1 h and a solution of N,O-dimethylhydroxylamine hydrochloride (1.51 g, 15.5 mol) and N-methylpyrrolidine (1.96 mL, 16.1 mmol) in anhydrous DCM (8 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred at

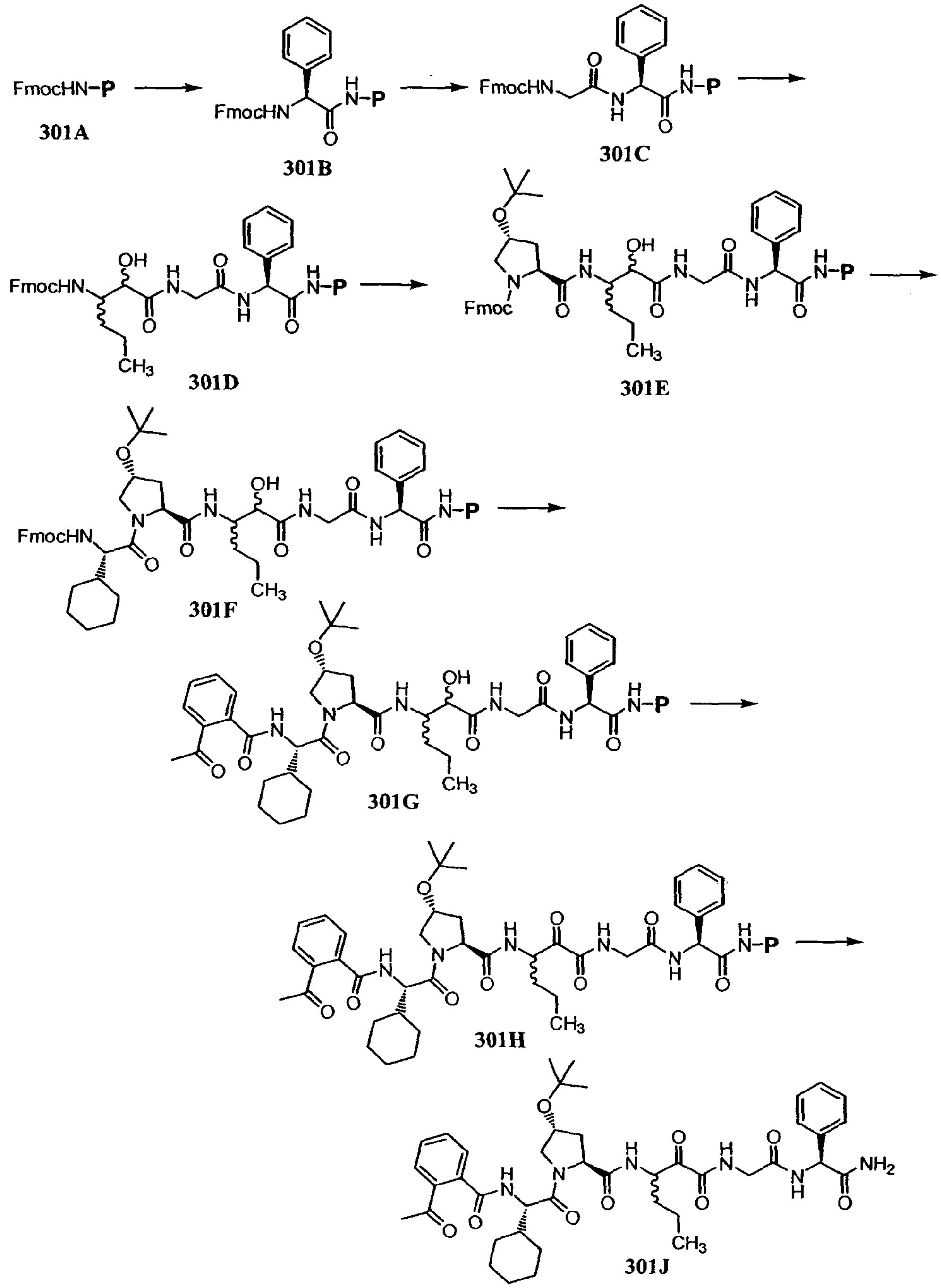
room temperature overnight. Toluene was added and the organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afforded compound **801B** (4 g, 9.29 mmol).

To a solution of Red-Al (6.28 mL, 21.4 mmol) in anhydrous toluene (8 mL) cooled to -20°C in a dry ice-acetone bath was added a solution of compound **801B** (4 g, 9.29 mmol) in anhydrous toluene (12 mL). The reaction mixture was stirred at –20 °C for 1.5 h. The organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product **801C** was used in the next reaction without further purification.

To a solution of compound **801C** (approx. 9.29 mmol) in hexane (15 mL) was added a solution of potassium cyanide (24 mg, 0.37 mmol) and tetrabutylammonium iodide (34 mg, 0.092 mmol) in water (4 mL) and acetone cyanohydrin (1.27 mL, 13.9 mmol) sequentially. The reaction mixture was stirred at room temperature for 24 h. Ethyl acetate was added and the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford compound **801D** (2.4 g, 6.03 mmol).

To a solution of compound **801D** (2.4 g, 6.03 mmol) in 1,4-dioxane (11 mL) was added concentrated hydrochloric acid (11 mL). The reaction mixture was heated at 80 °C for 3 h. Ethyl acetate (25 mL) and water (25 mL) was added. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the desired compound **801** as a white foamy solid (2 g, 4.8 mmol). MS (LCMS-Electrospray) 418.1 MH^+.

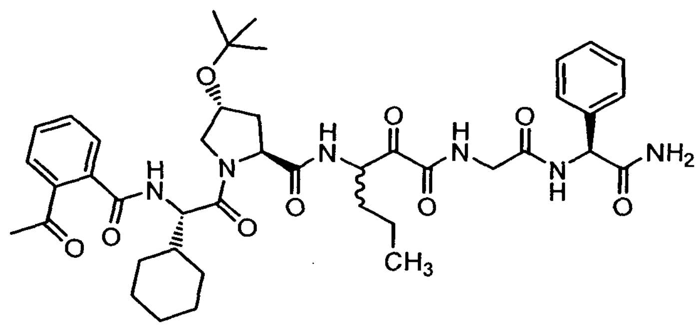
Scheme 8



301A 301B 301C 301D 301E 301F 301G 301H 301J

Example (301J):

Scheme 8 Compound (301J)

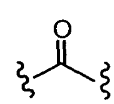


(301J)

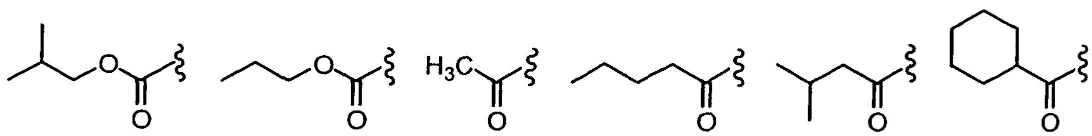
Resin-bound compound **301B**, **301C**, **301D**, **301E**, **301F** and **301G** were prepared according to the general procedure for solid-phase coupling reactions started with 100 mg of Fmoc-Sieber resin (0.03 mmol). Resin-bound compound **301G** was oxidized to resin-bound compound **301H** according to the general procedure for solid-phase Dess-Martin oxidation. The resin-bound compound **301H** was treated with 4 mL of a 2 % v/v solution of TFA in DCM for 5 min. The filtrate was added to 1 mL of AcOH and the solution was concentrated by vacuum centrifugation to provide compound **301J** (0.0069 g, 29 % yield). MS (LCMS-Electrospray) 771.2 MH^+.

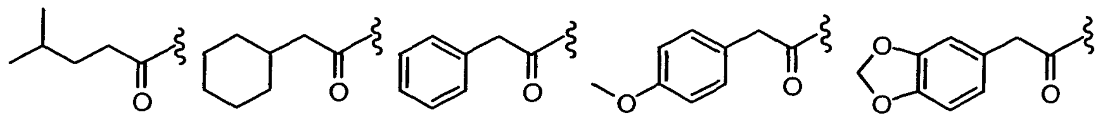
Using the solid phase synthesis techniques detailed above, and the following moieties for the various functionalities in the compound of Formula 1, the compounds in **Table 3** were prepared:

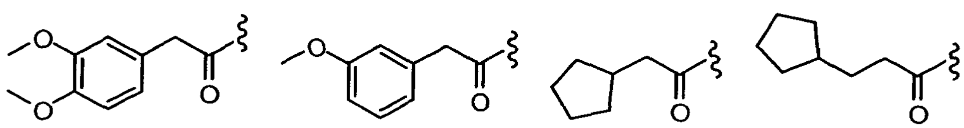
-W-:

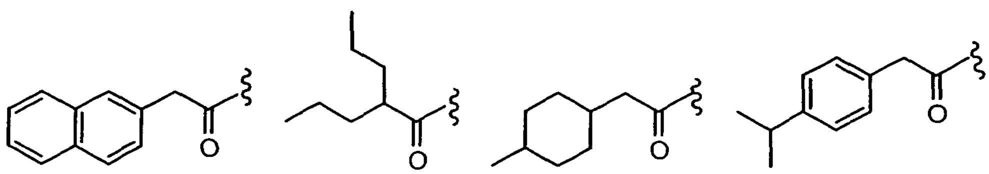


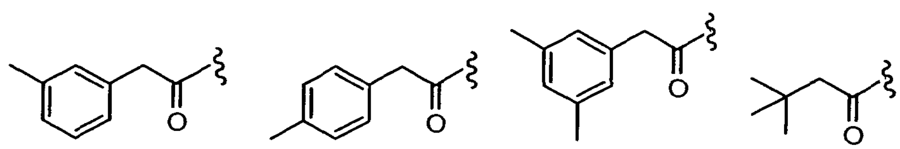
Y-W-:

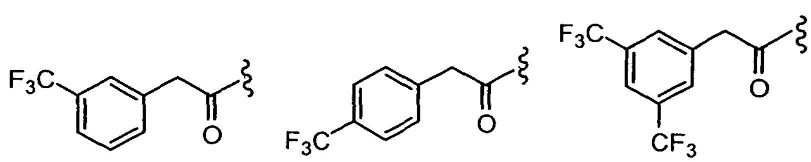


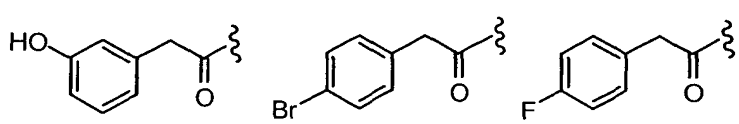


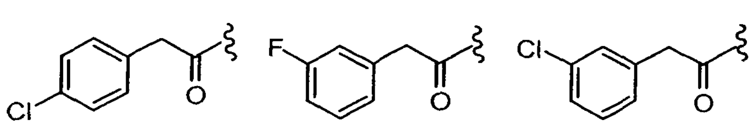


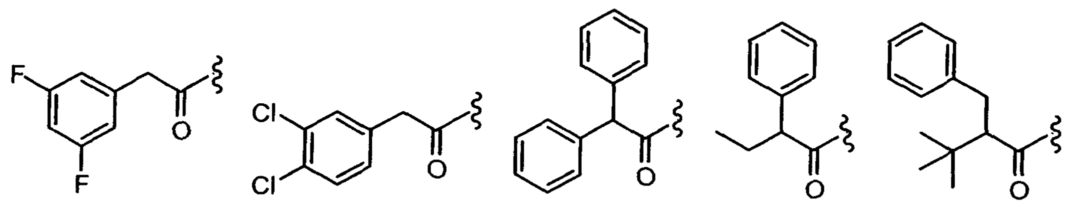


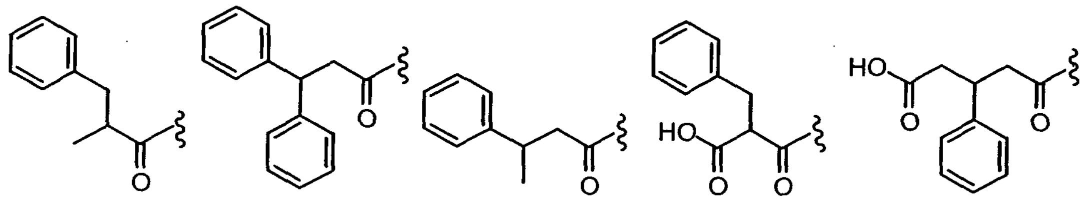


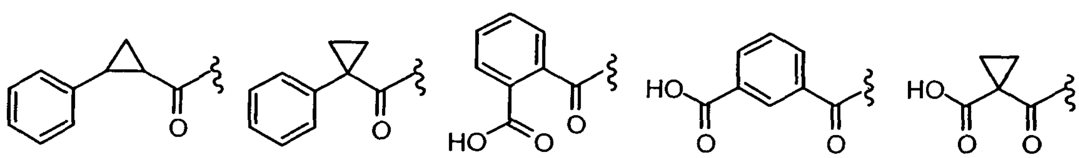


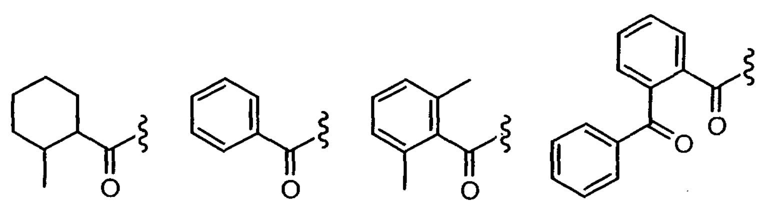


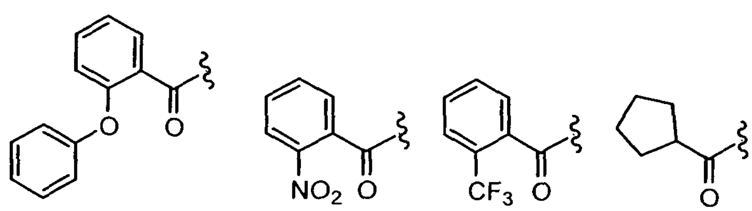


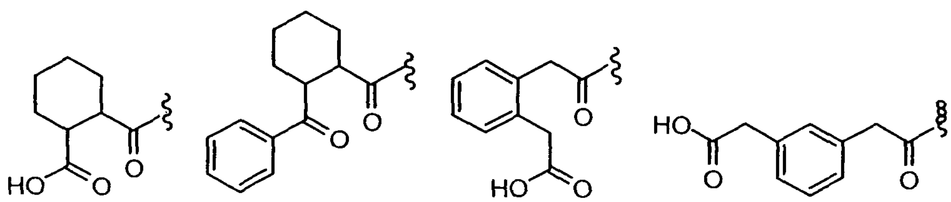


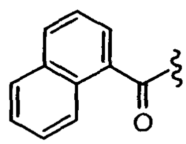
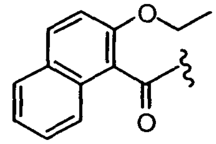
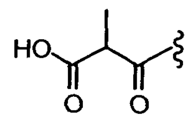
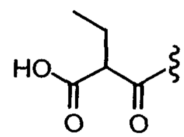
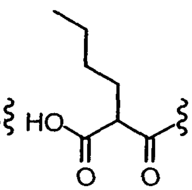


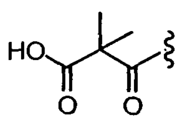
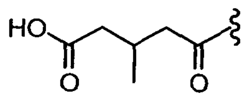
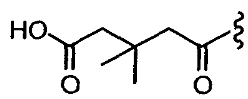
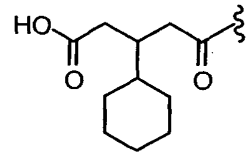


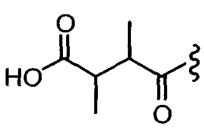
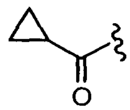
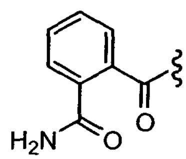
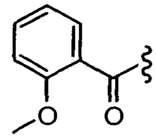
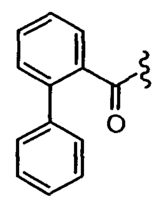
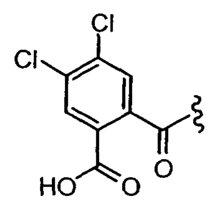


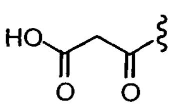
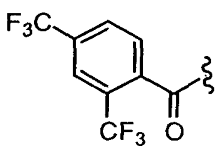
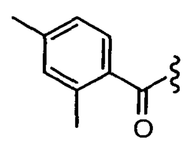
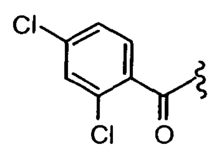
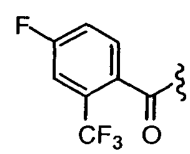


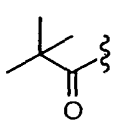
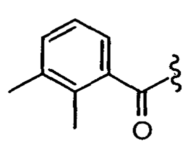
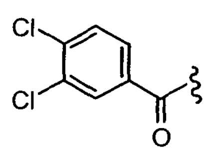
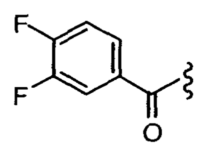
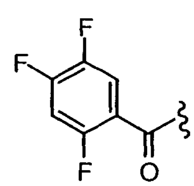


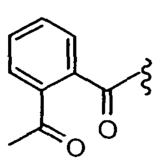
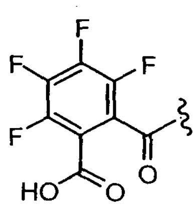
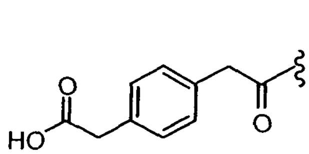
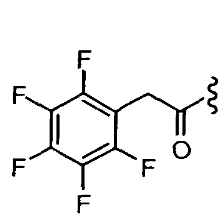
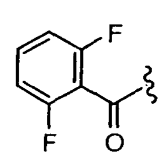
    

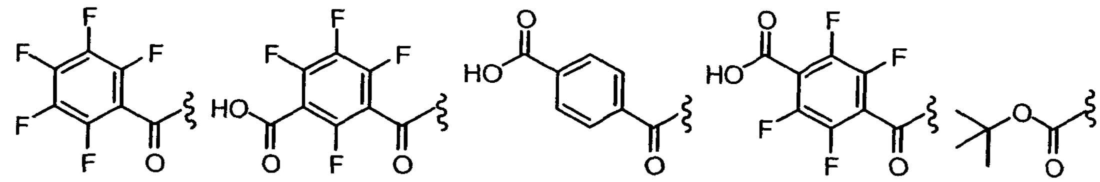
   

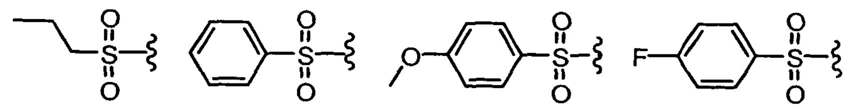
     





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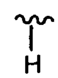
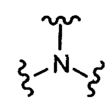
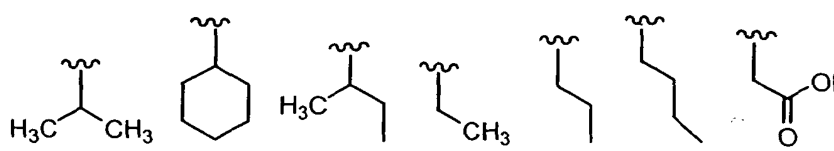
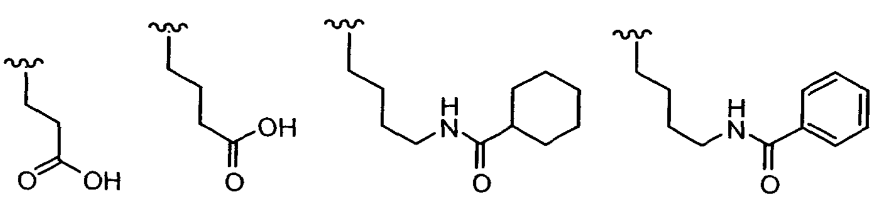


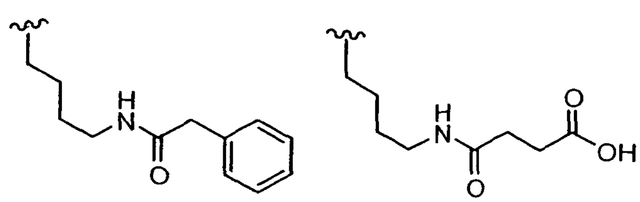
-Z-:

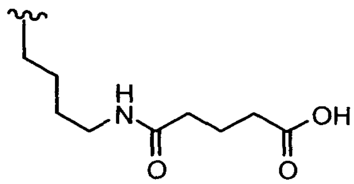
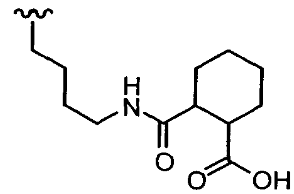
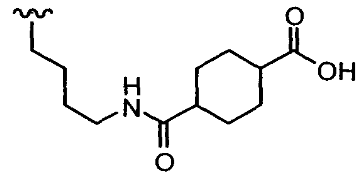


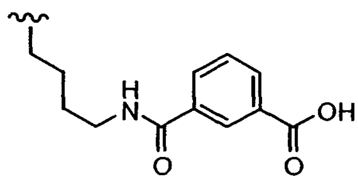
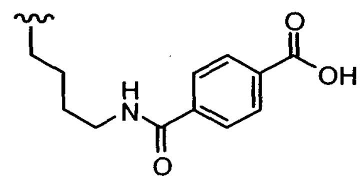
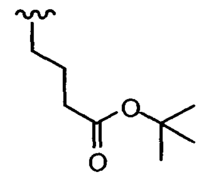
-R³:

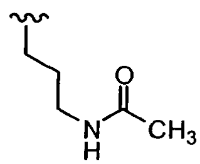
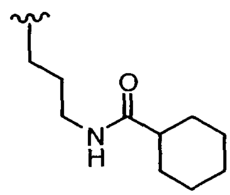
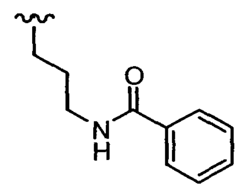


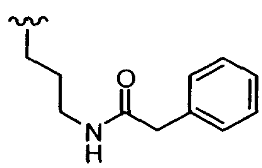
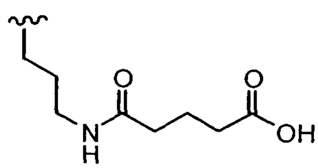
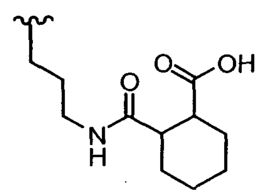


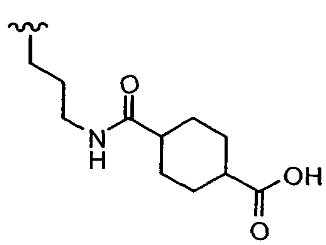
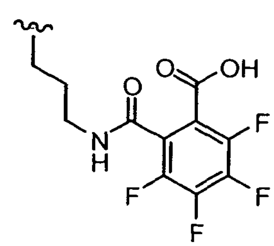
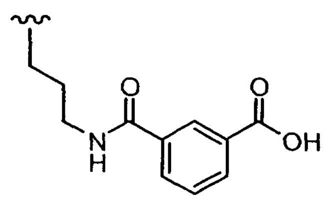


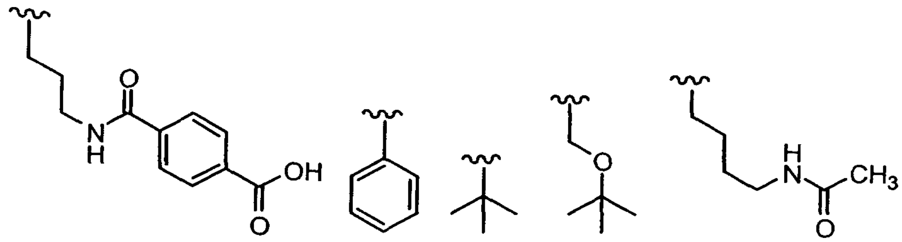




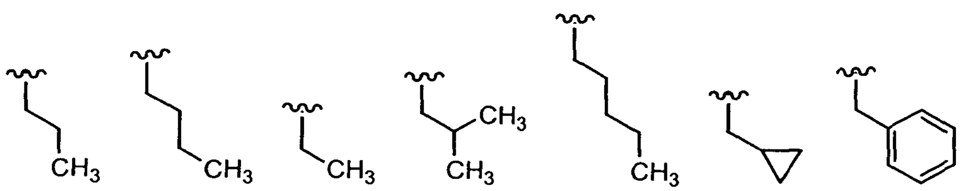




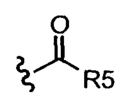






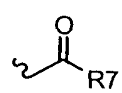
-R^2:



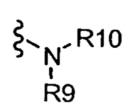
-R^1:



-R^5:

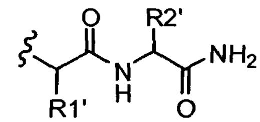


-R^7:

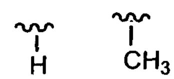


-R^9:

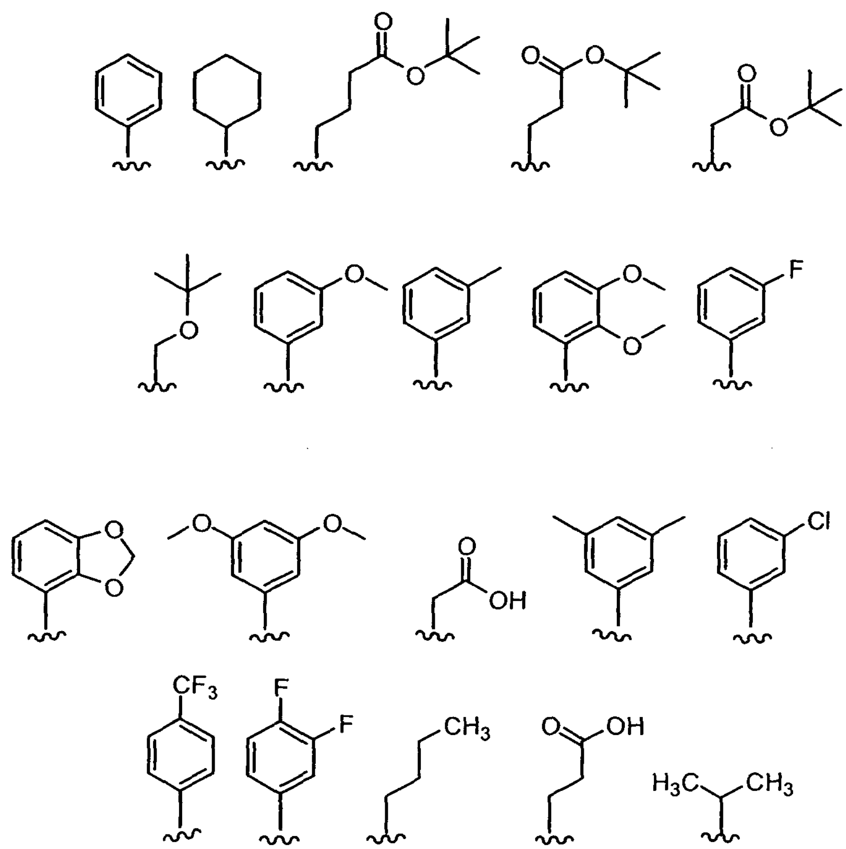
$-R^{10}$:


O
R2'
NH2
N
H
R1'
O

$-R^{1'}$:


H
CH3

$-R^{2'}$:


O
O
O
O
O
O
O
O
O
O
F
O
O
O
O
O
OH
Cl
F
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O
OH
H3C
CH3

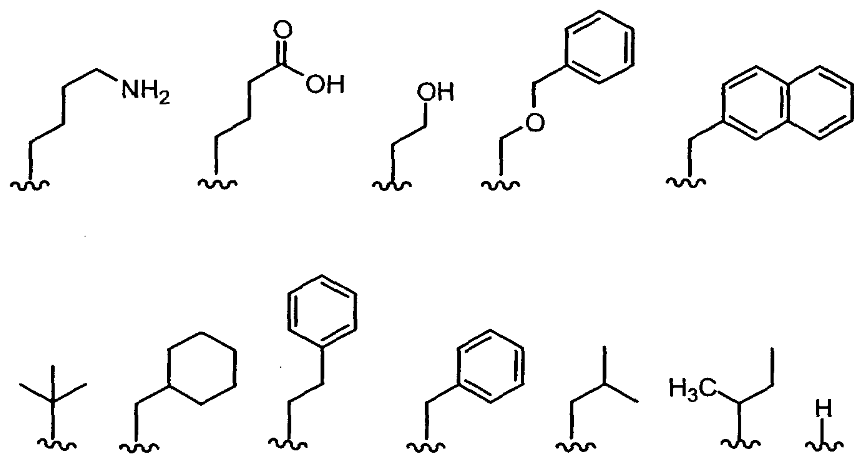
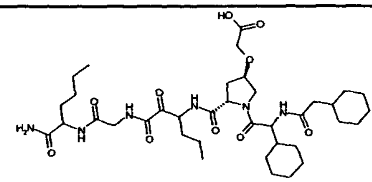
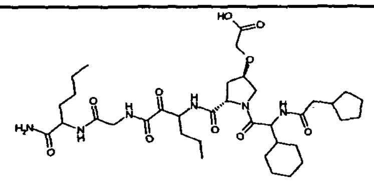
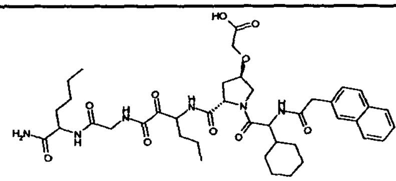
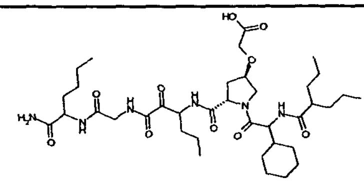
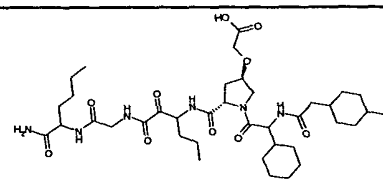
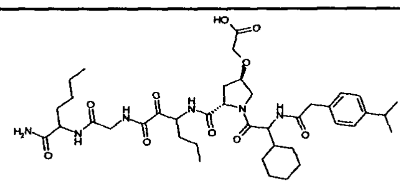
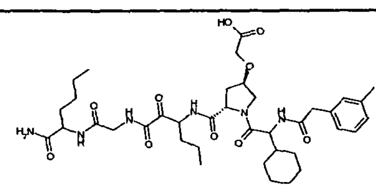
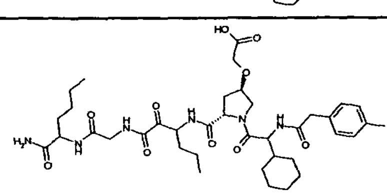


Table 3. Compounds prepared by Solid Phase Synthesis

STRUCTURE	Ki* CLASS
	C
	C
	C
	C
	C
	C
	C
	C

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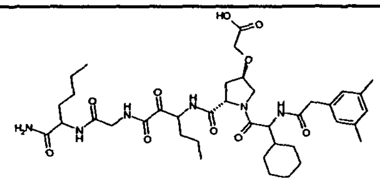
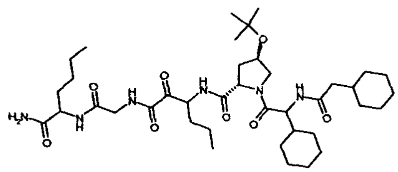
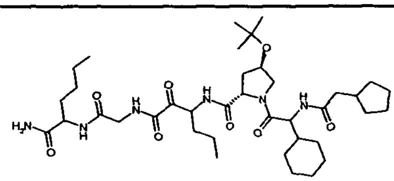
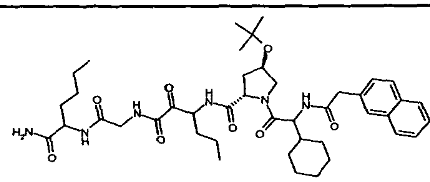
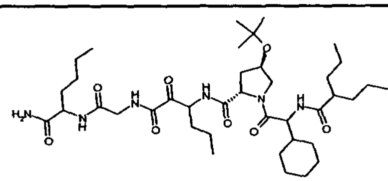
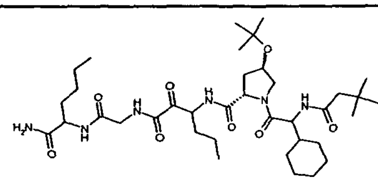
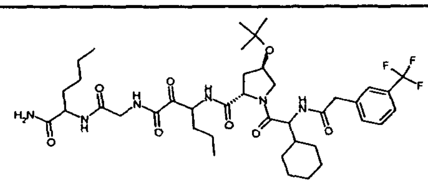
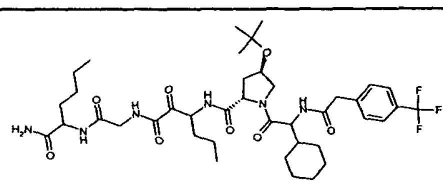
	C
	B
	B
	C
	B
	C
	B
	B

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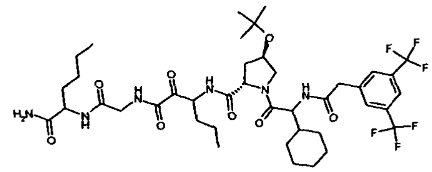
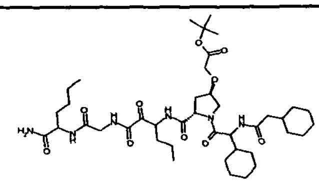
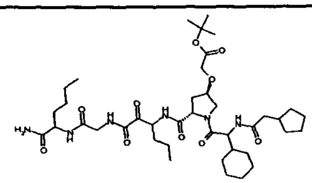
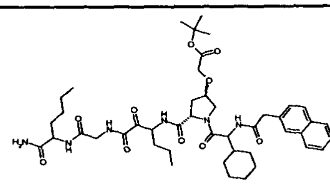
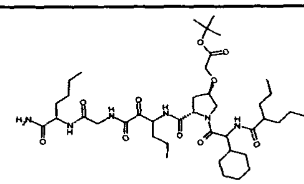
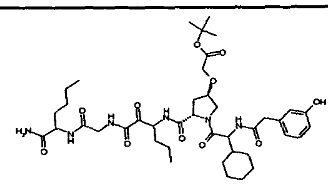
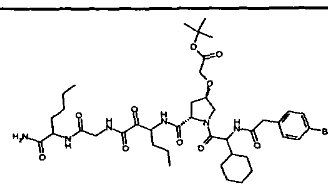
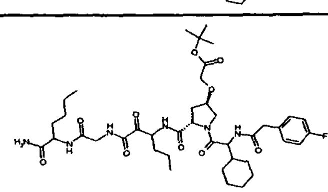
	C
	C
	C
	C
	C
	C
	C
	C

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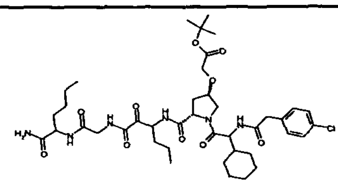
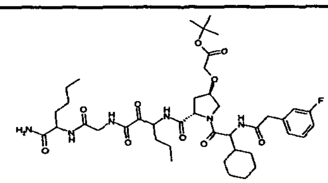
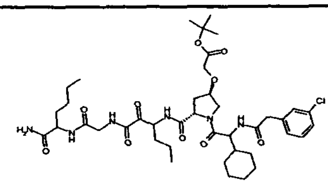
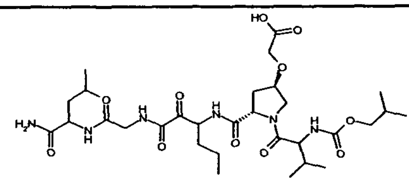
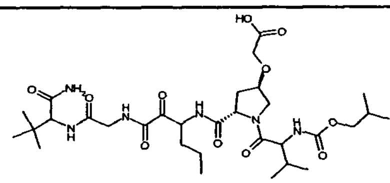
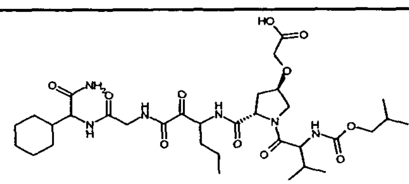
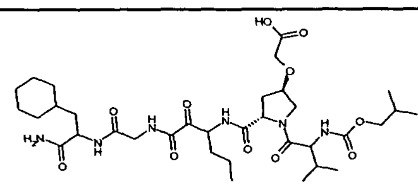
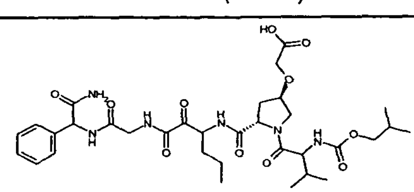
	C
	C
	C
	C
	C
	C
	C
	C

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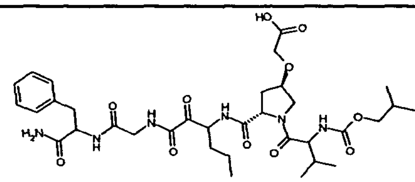
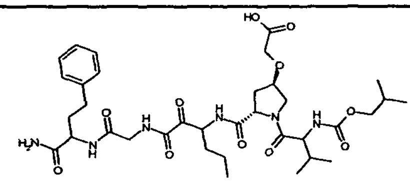
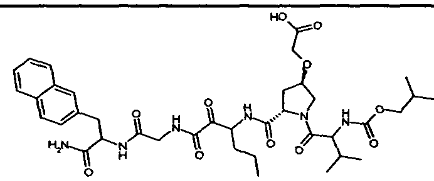
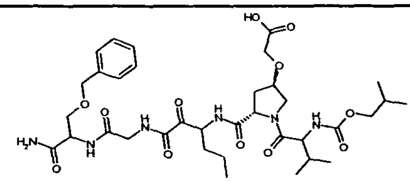
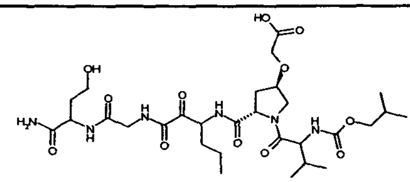
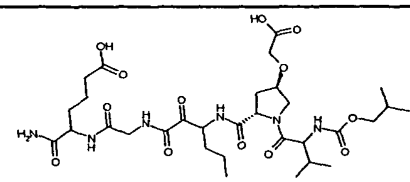
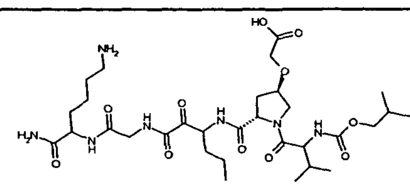
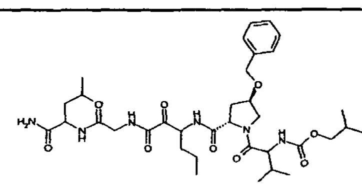
	C
	C
	C
	C
	C
	C
	C
	C

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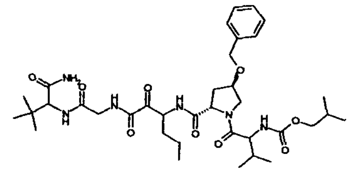
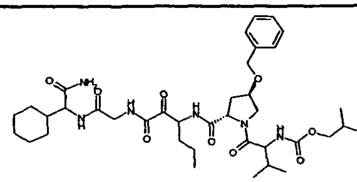
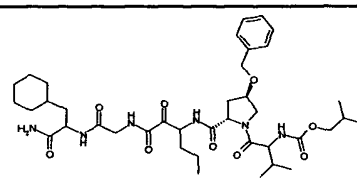
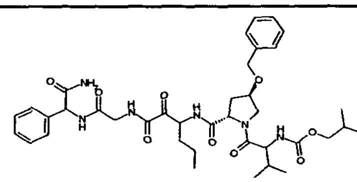
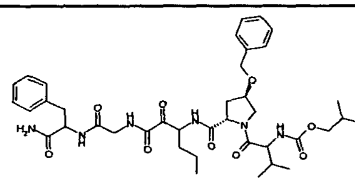
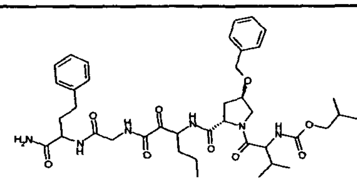
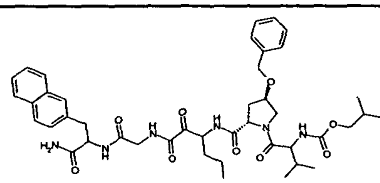
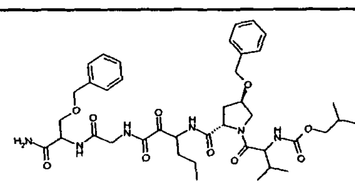
	C
	B
	C
	B
	C
	C
	C
	C

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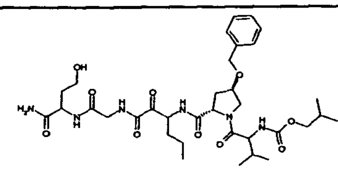
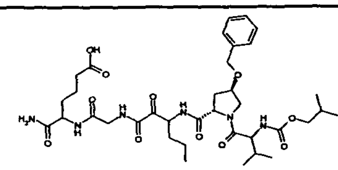
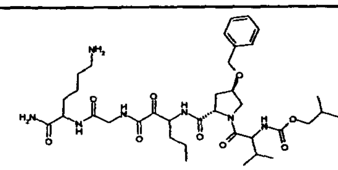
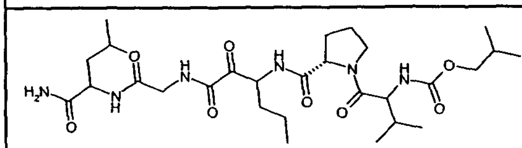
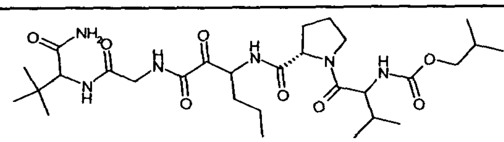
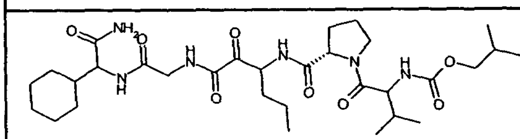
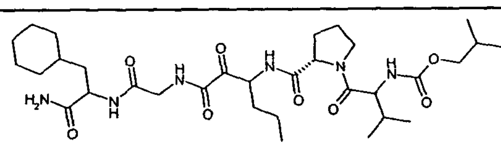
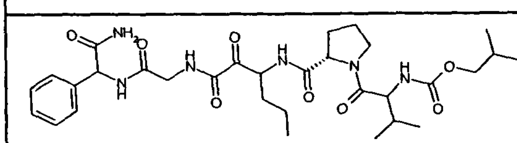
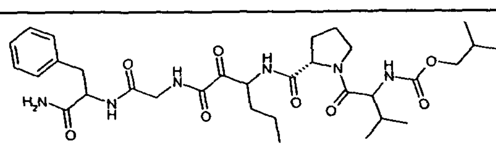
	C
	C
	C
	C
	C
	C
	C
	C
	C

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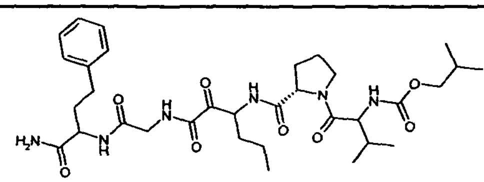
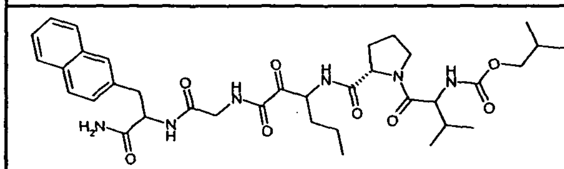
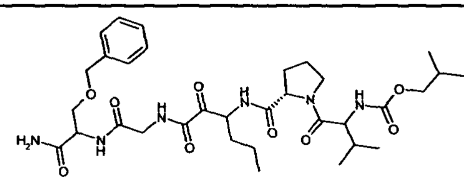
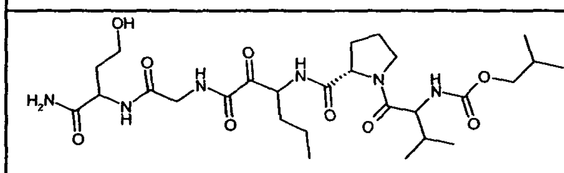
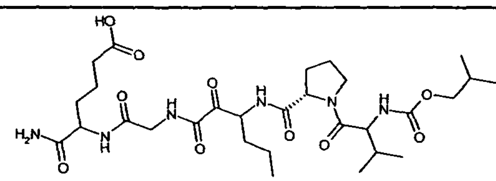
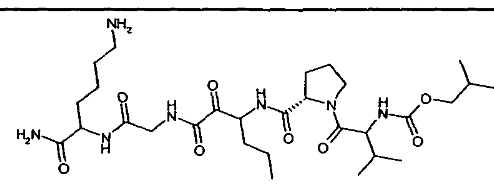
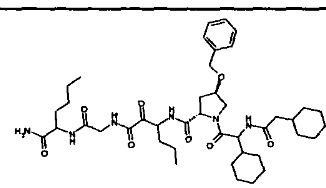
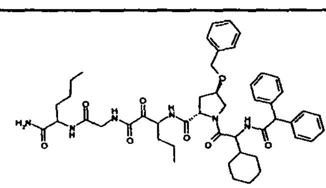
	C
	C
	C
	C
	C
	C
	B
	B

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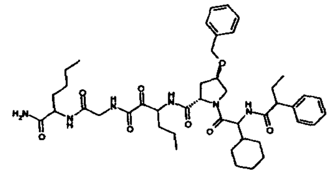
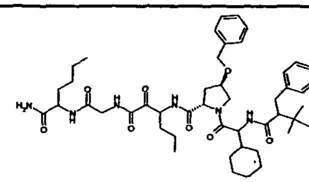
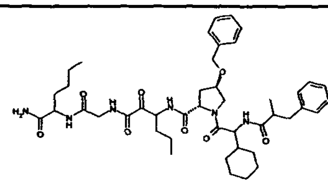
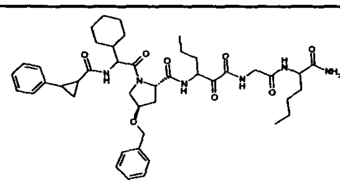
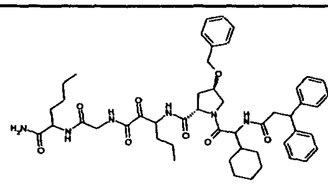
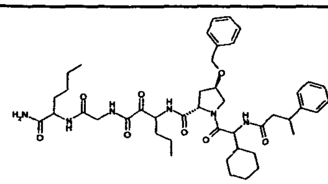
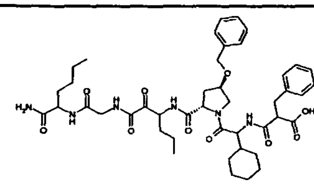
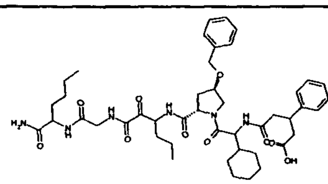
	B
	C
	C
	C
	C
	C
	C
	C

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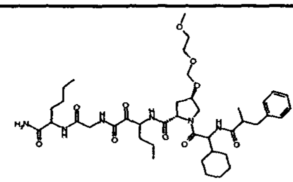
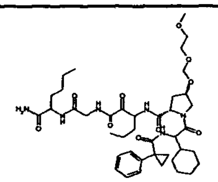
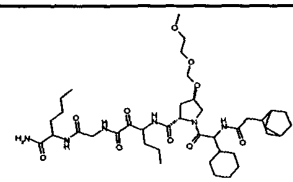
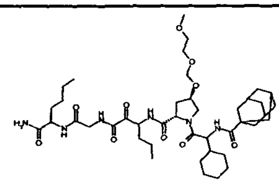
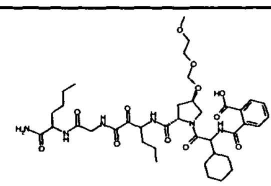
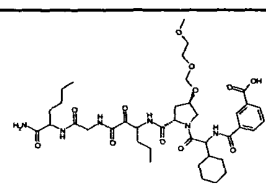
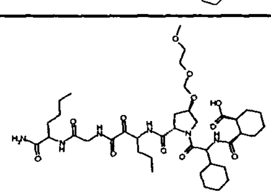
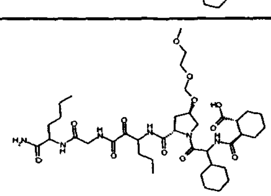
	C
	C
	B
	C
	B
	C
	B
	B

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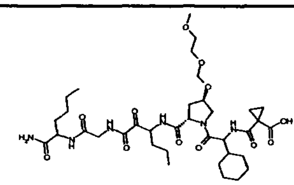
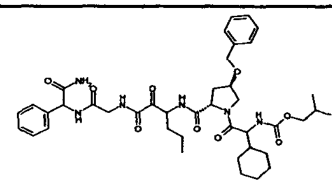
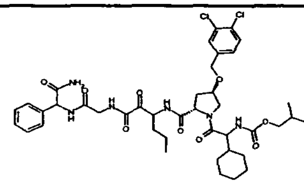
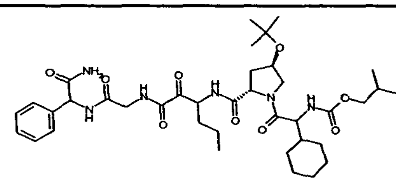
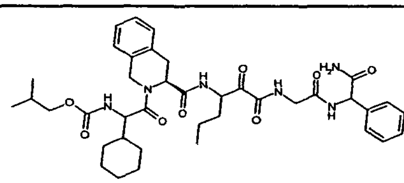
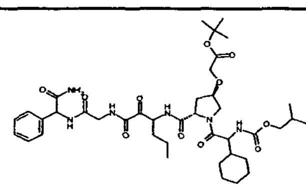
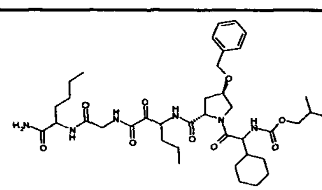
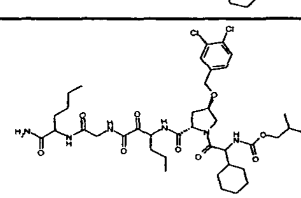
	C
	A
	A
	A
	B
	A
	B
	B

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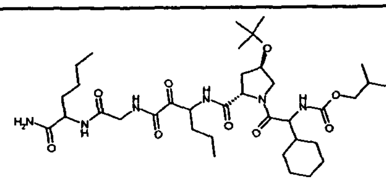
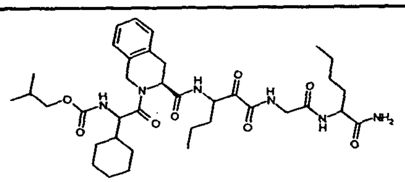
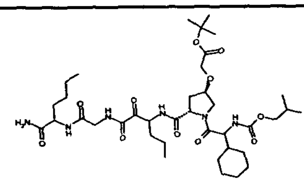
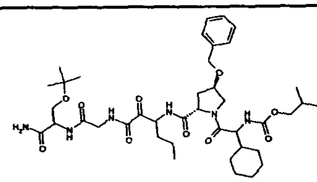
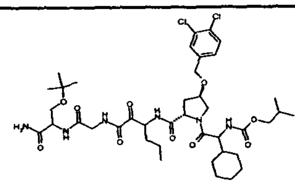
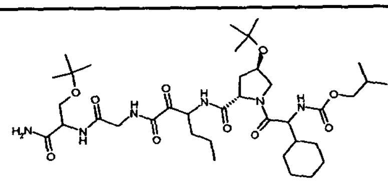
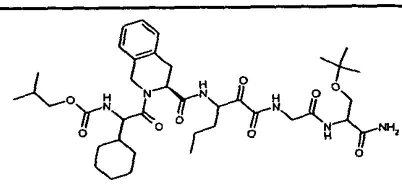
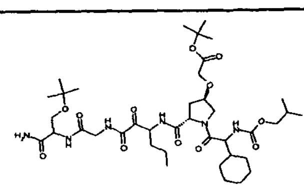
	B
	C
	B
	B
	B
	B
	C
	B

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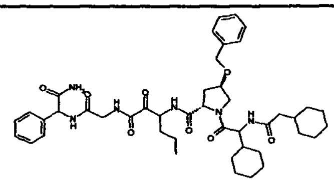
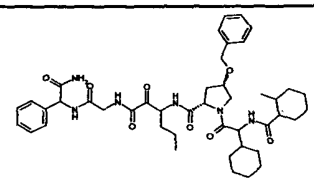
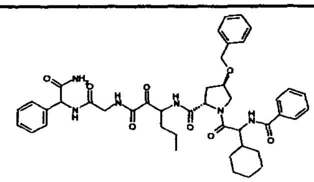
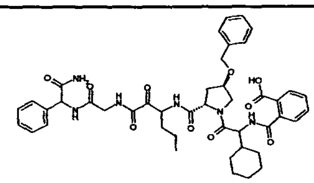
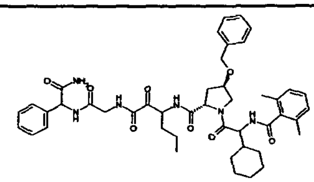
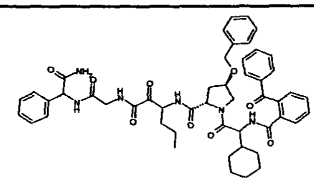
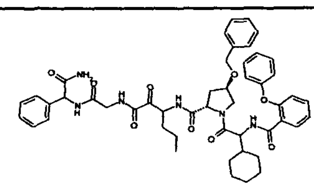
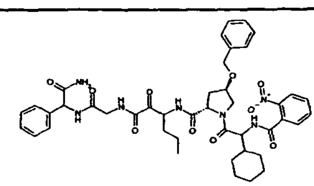
	B
	B
	B
	B
	B
	C
	C
	A

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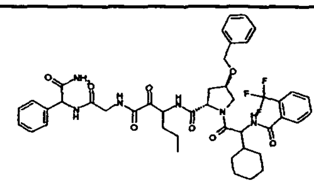
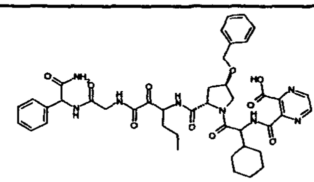
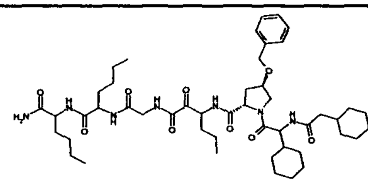
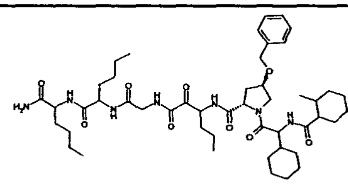
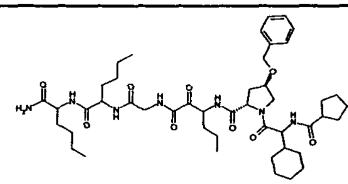
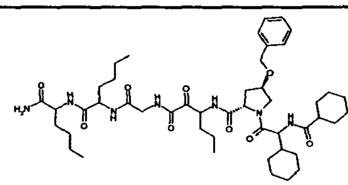
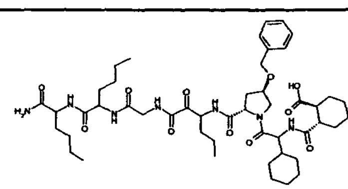
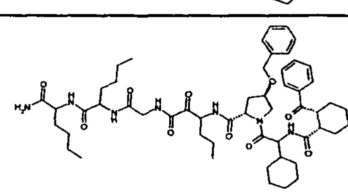
	B
	B
	B
	B
	B
	B
	B
	C

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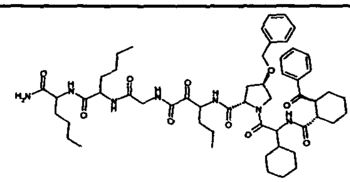
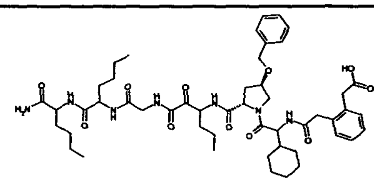
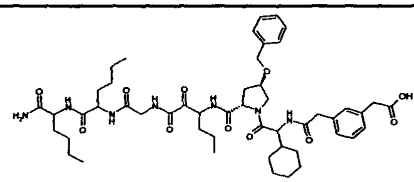
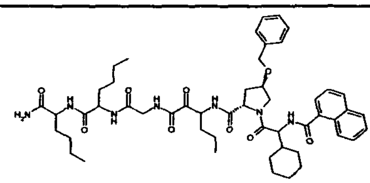
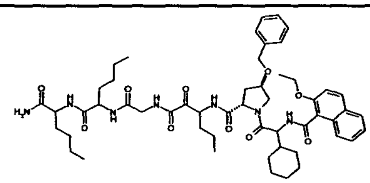
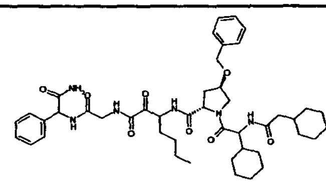
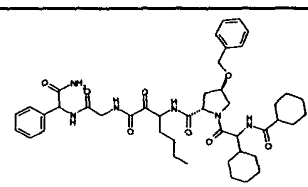
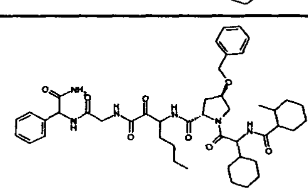
	B
	B
	B
	B
	B
	A
	B
	B

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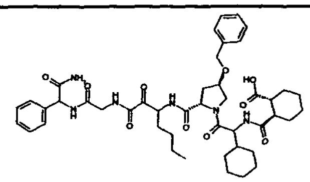
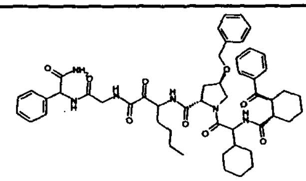
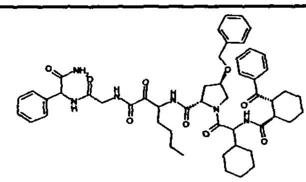
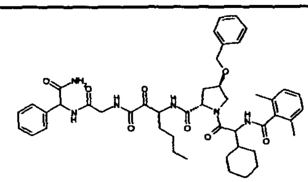
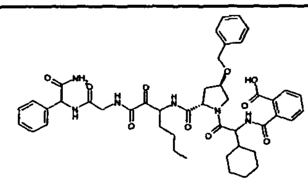
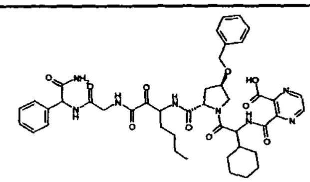
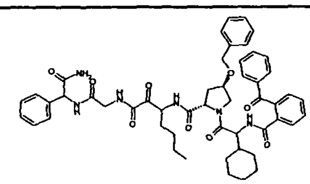
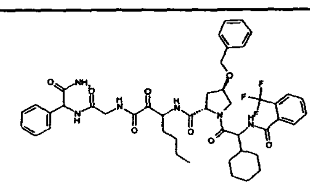
	B
	B
	C
	B
	B
	B
	B
	B

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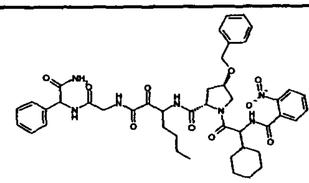
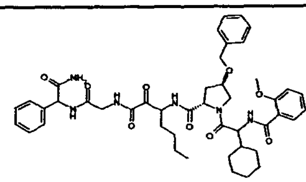
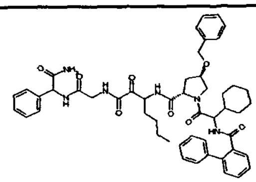
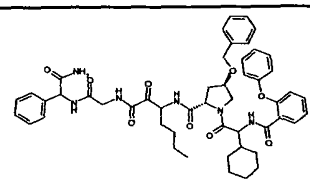
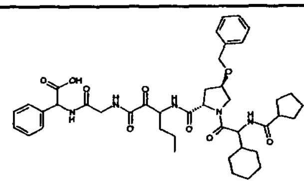
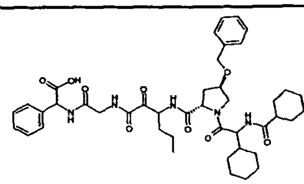
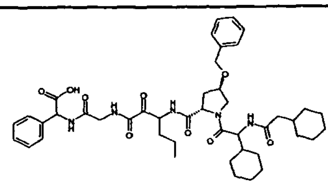
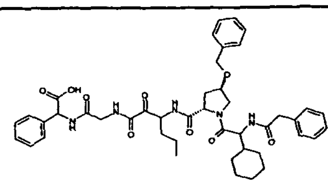
	B
	C
	C
	C
	A
	B
	A
	A

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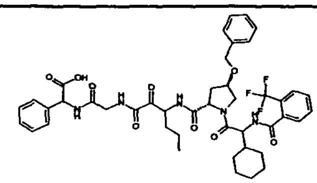
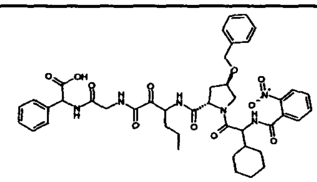
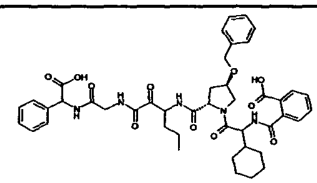
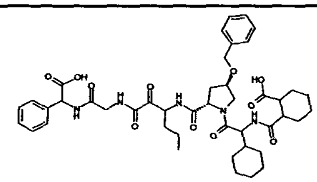
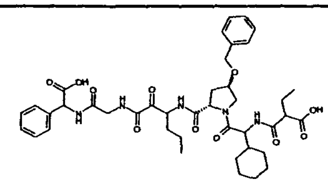
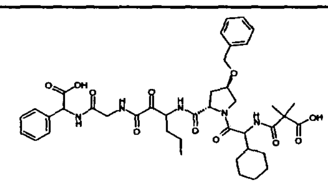
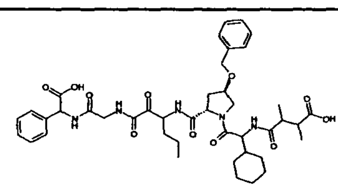
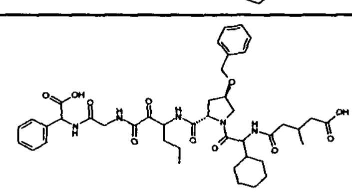
	B
	A
	A
	A
	A
	B
	B
	A

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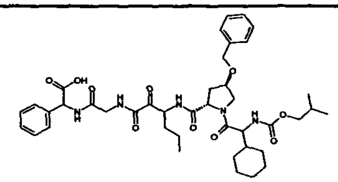
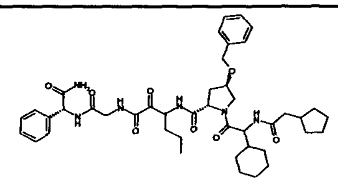
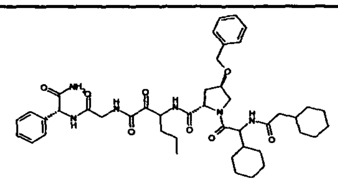
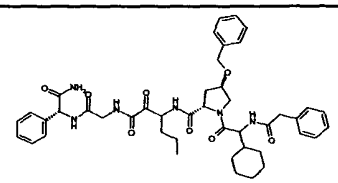
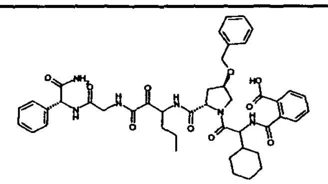
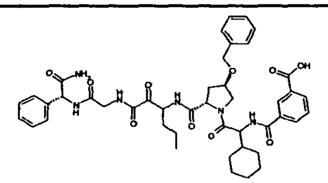
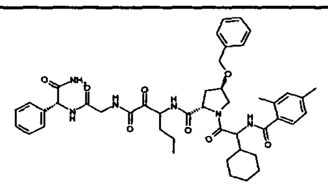
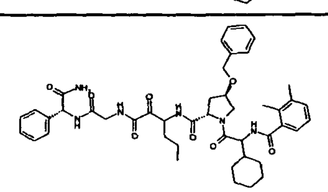
	A
	B
	B
	C
	B
	B
	B
	B

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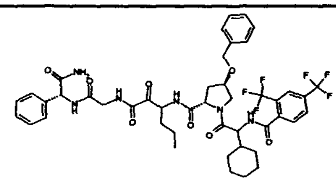
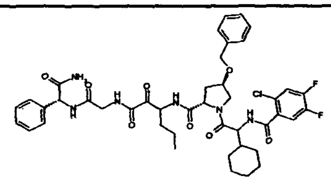
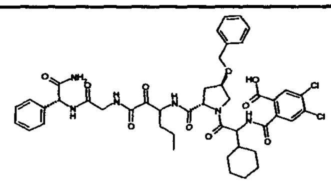
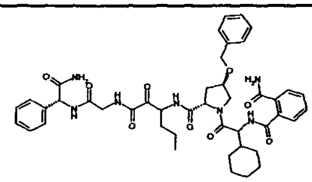
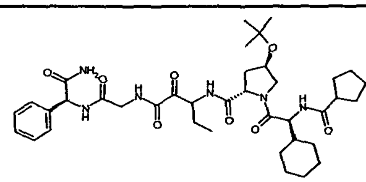
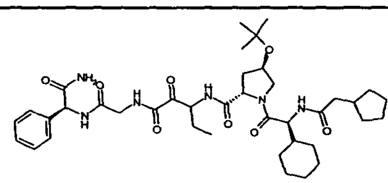
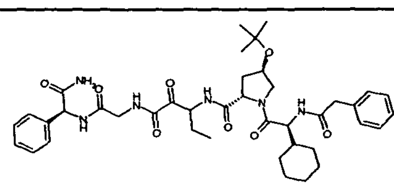
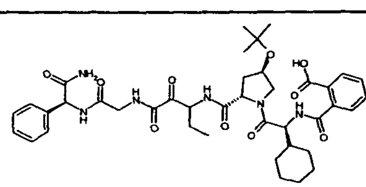
	C
	C
	C
	C
	B
	B
	B
	B

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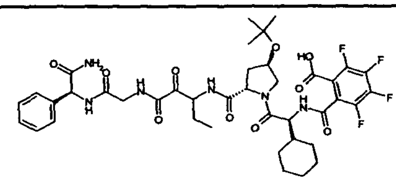
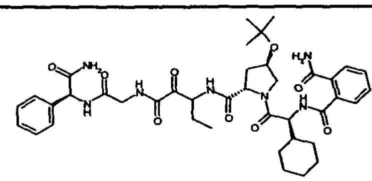
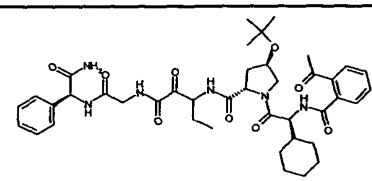
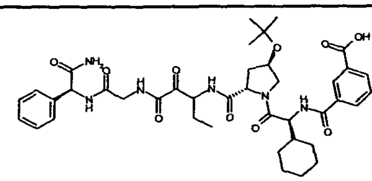
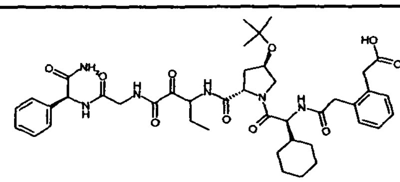
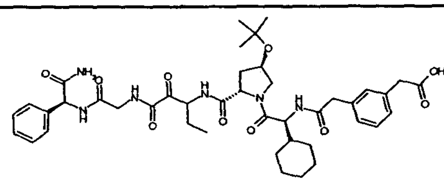
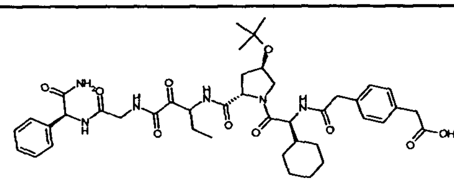
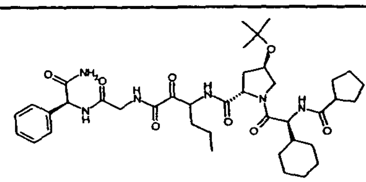
	A
	B
	C
	C
	B
	B
	B
	B

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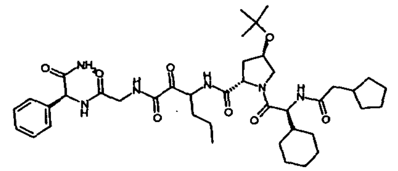
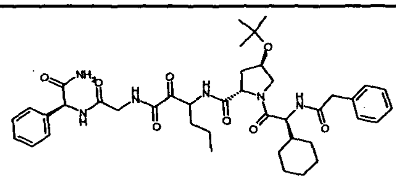
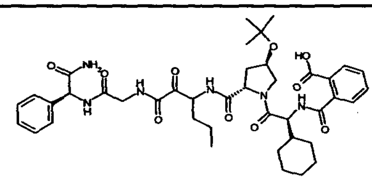
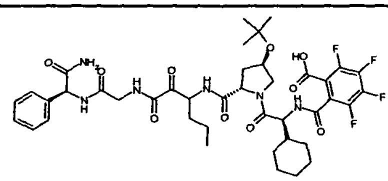
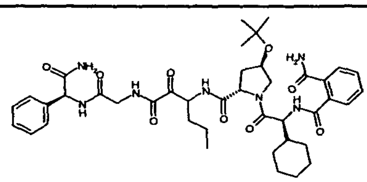
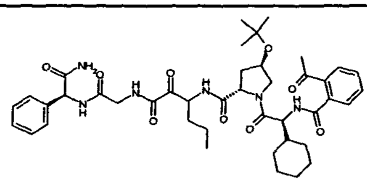
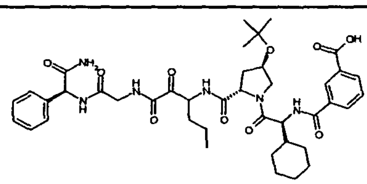
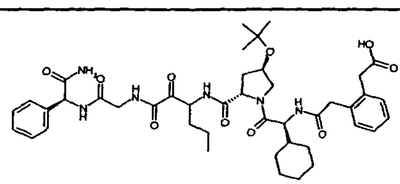
	A
	A
	A
	A
	B
	C
	B
	A

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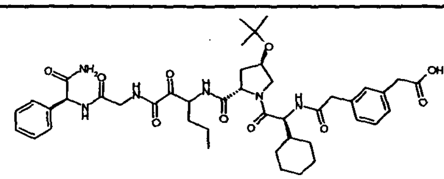
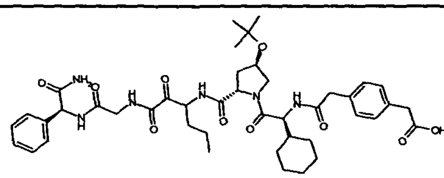
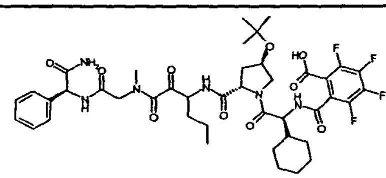
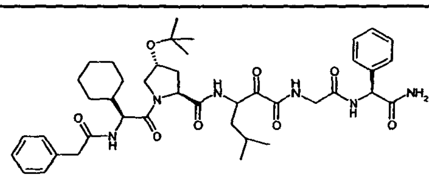
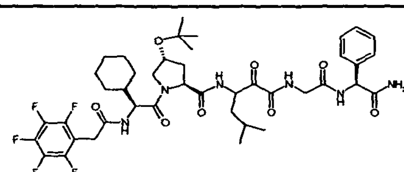
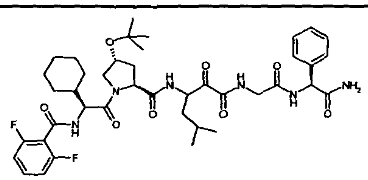
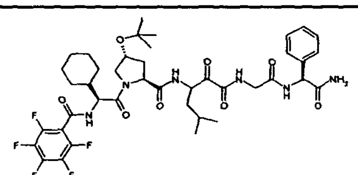
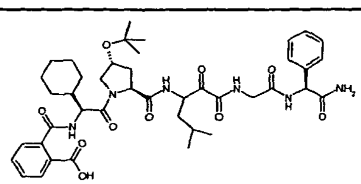
	C
	A
	C
	C
	C
	C
	C
	C

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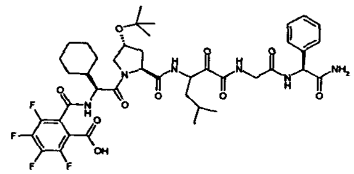
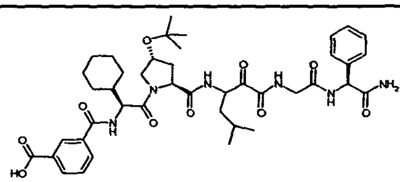
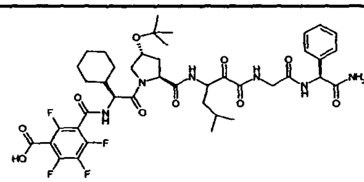
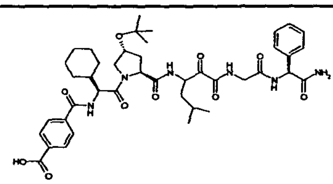
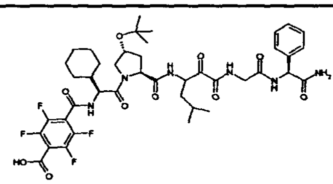
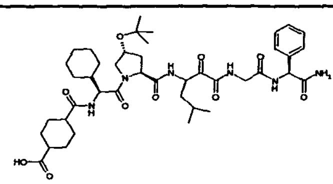
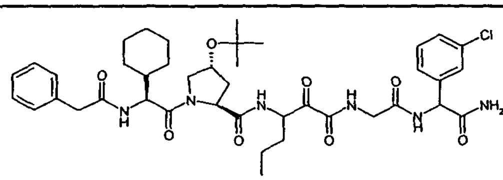
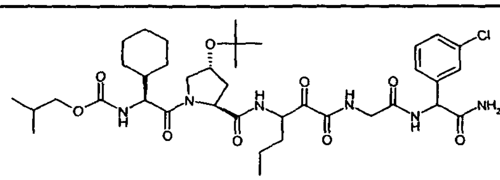
	C
	C
	C
	C
	C
	C
	B
	B

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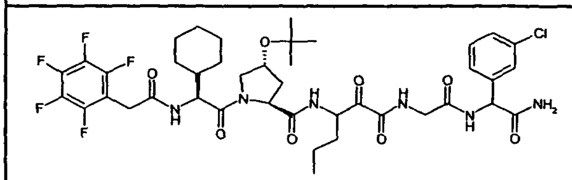
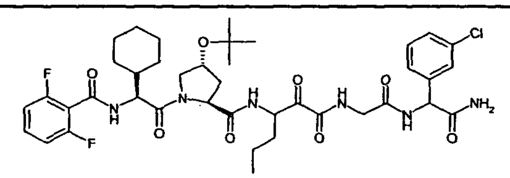
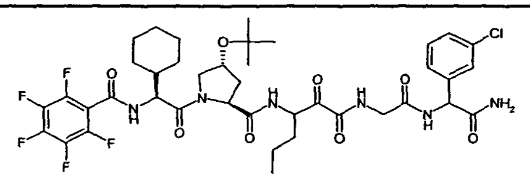
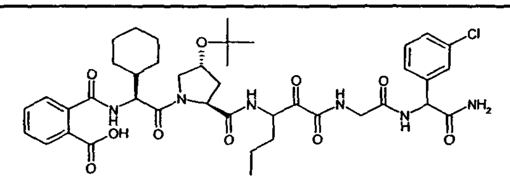
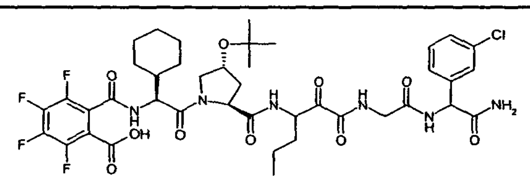
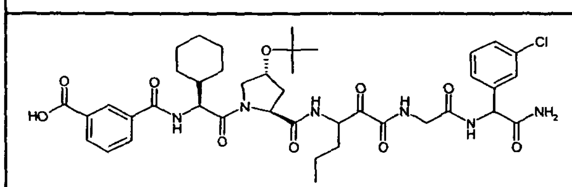
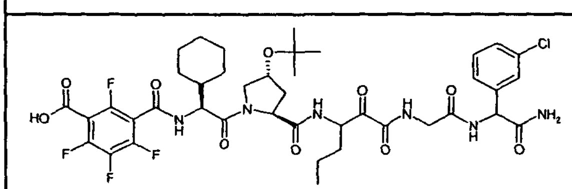
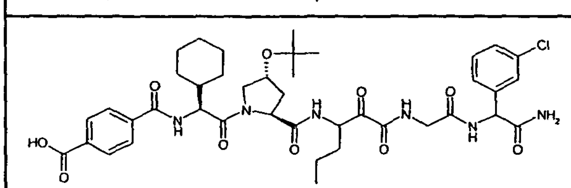
	B
	B
	C
	B
	A
	B
	B
	B

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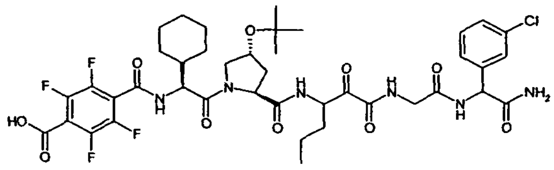
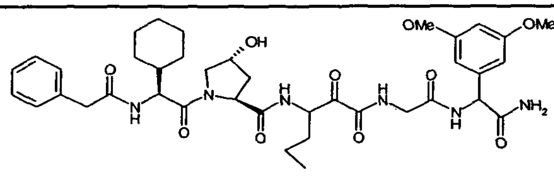
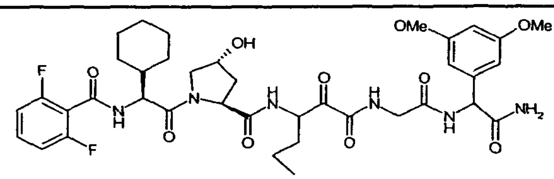
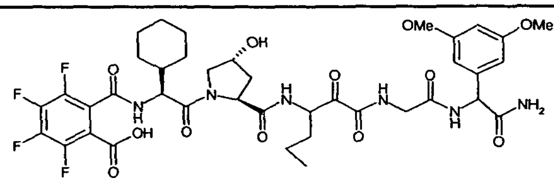
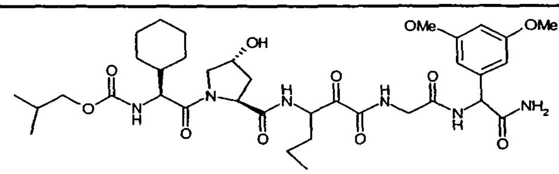
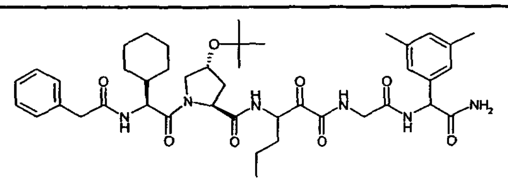
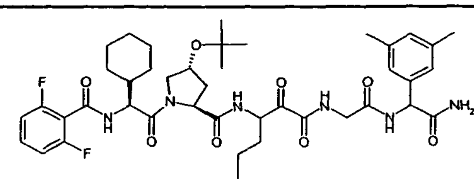
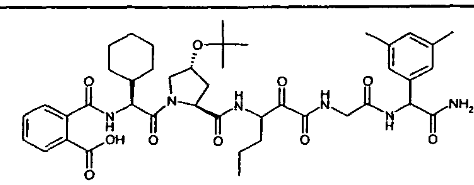
	B
	B
	B
	B
	B
	B
	B
	B

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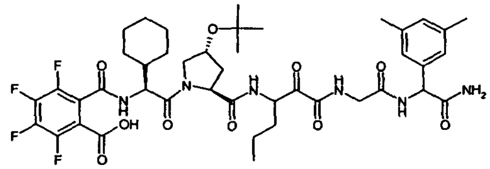
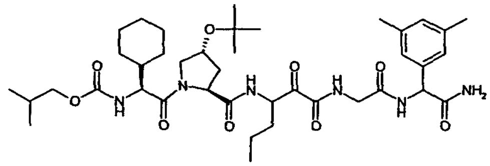
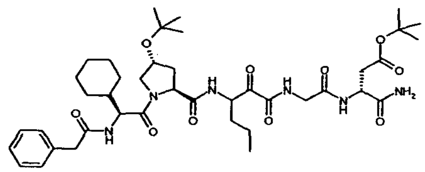
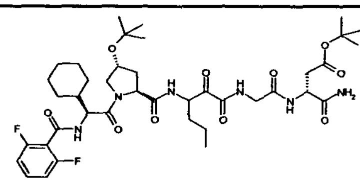
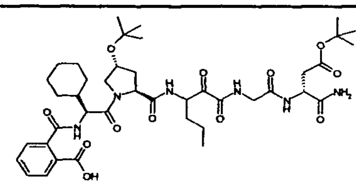
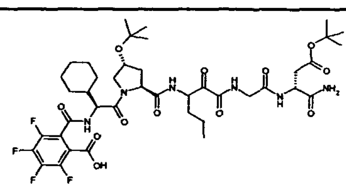
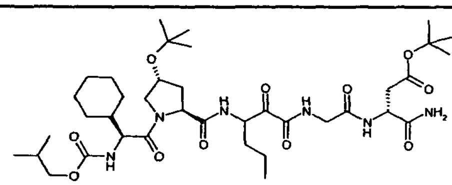
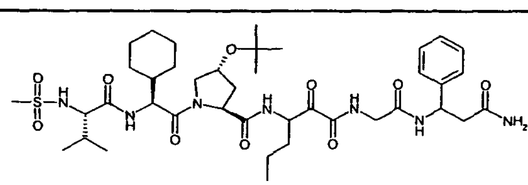
	A
	B
	C
	C
	C
	C
	C
	B

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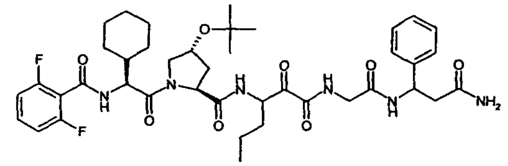
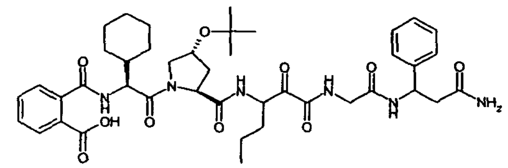
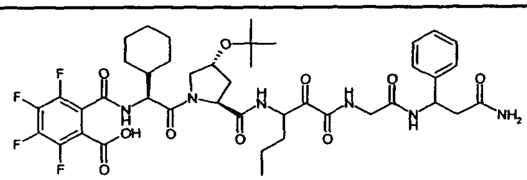
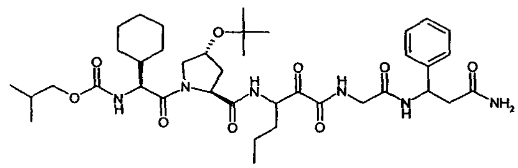
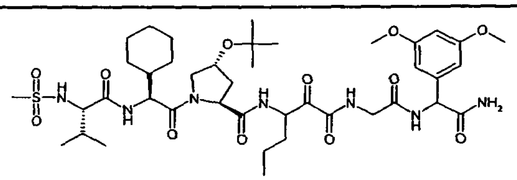
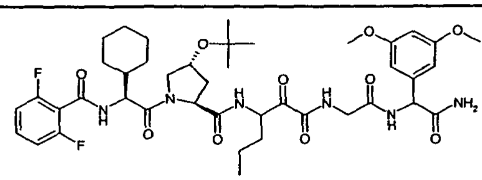
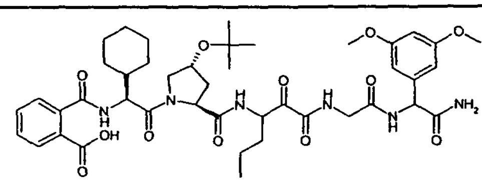
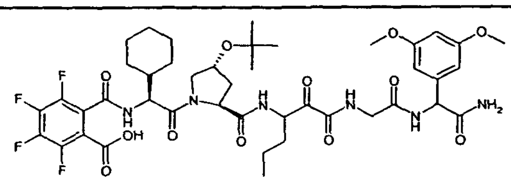
	C
	C
	B
	C
	B
	B
	B
	B

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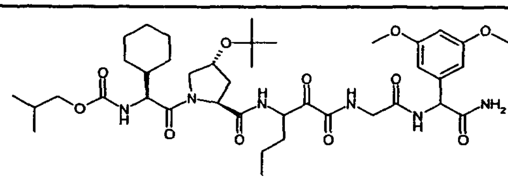
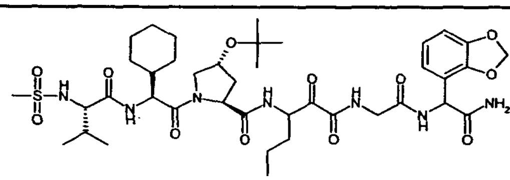
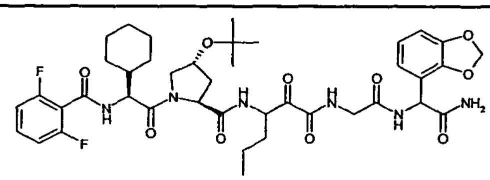
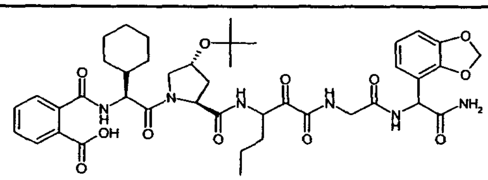
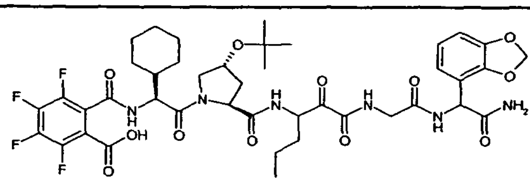
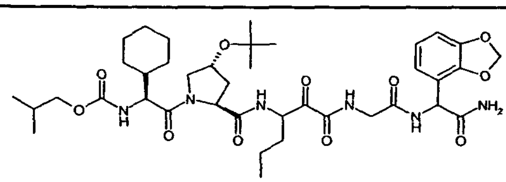
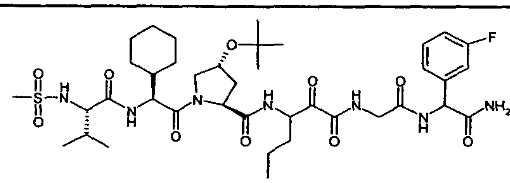
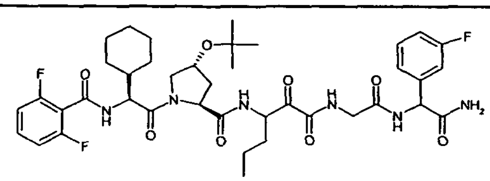
	B
	B
	B
	B
	B
	B
	B
	B

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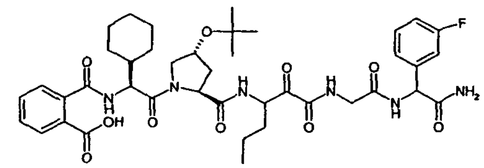
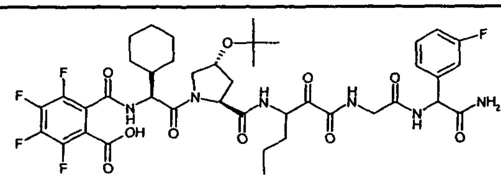
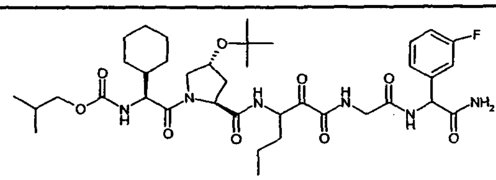
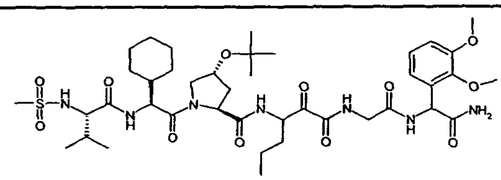
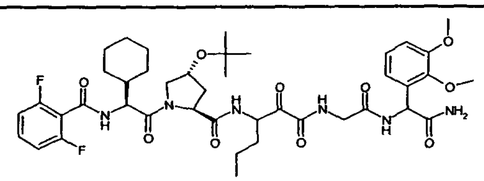
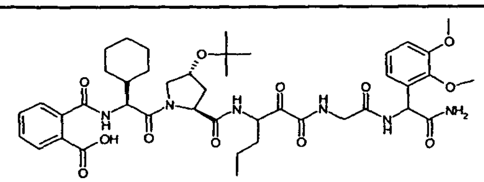
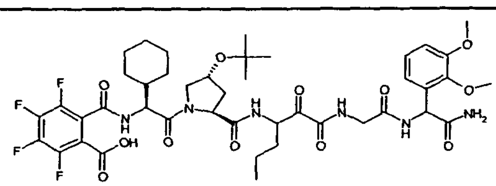
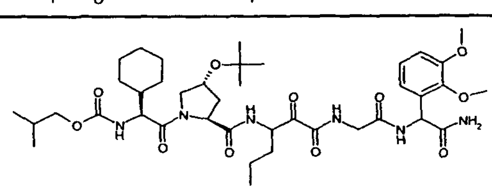
	B
	B
	B
	B
	B
	B
	B
	B

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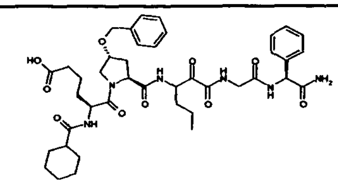
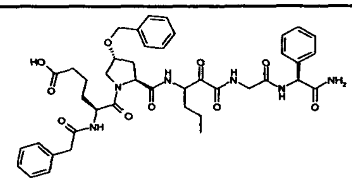
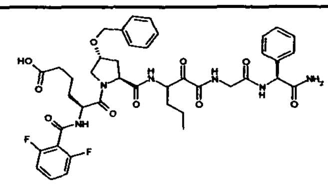
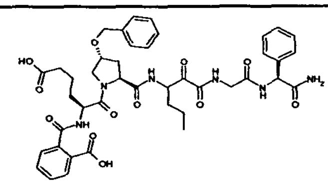
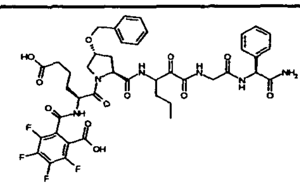
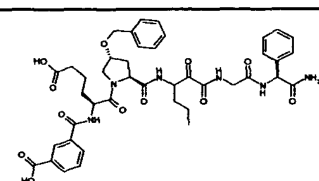
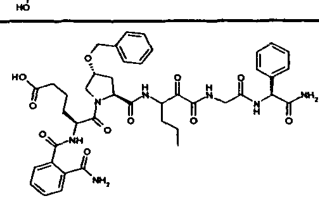
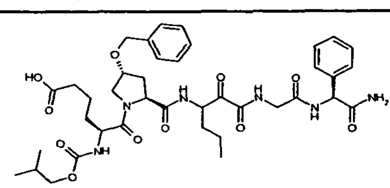
	B
	B
	B
	B
	B
	C
	B
	B

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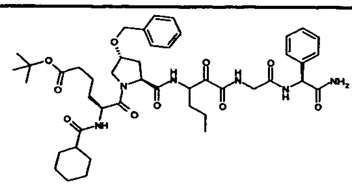
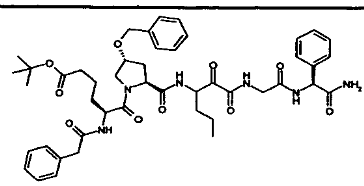
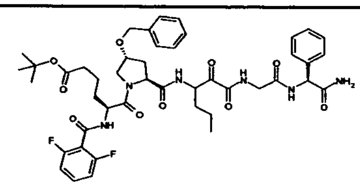
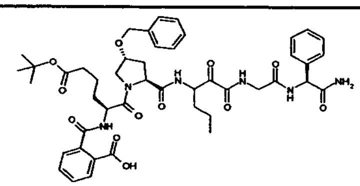
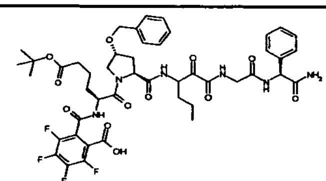
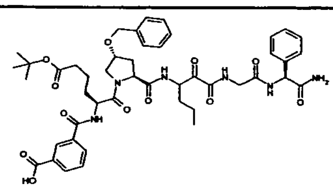
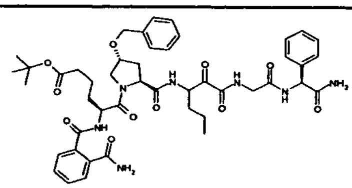
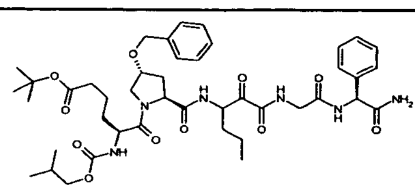
	C
	C
	C
	C
	B
	C
	C
	C

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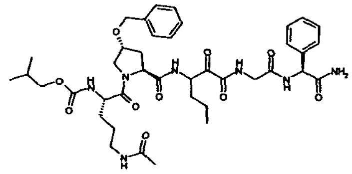
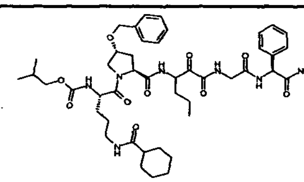
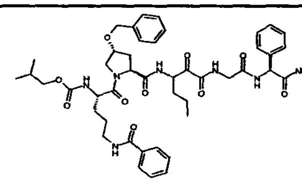
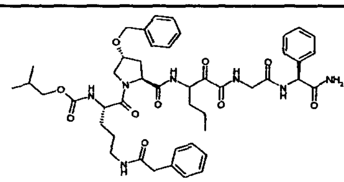
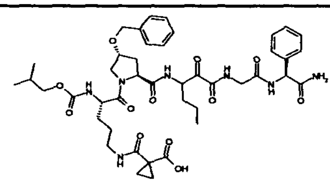
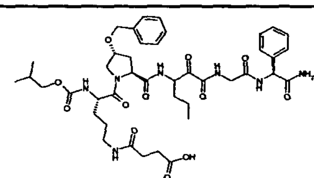
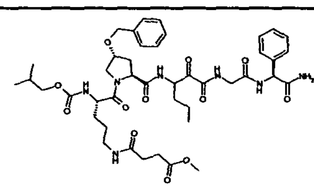
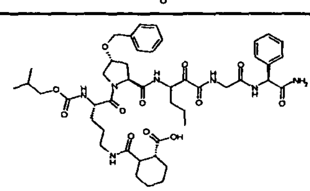
	C
	C
	C
	C
	C
	C
	C
	C

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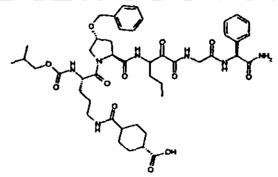
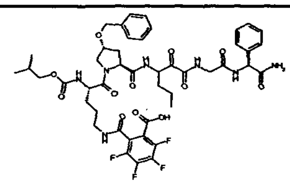
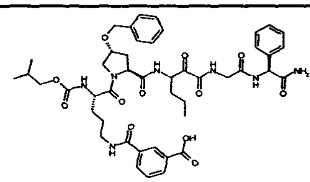
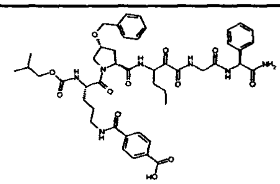
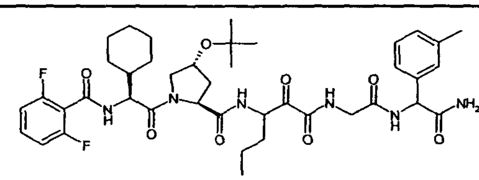
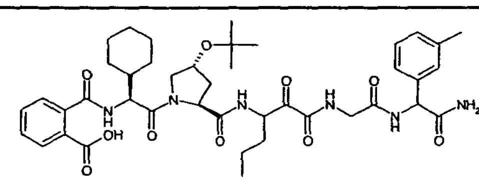
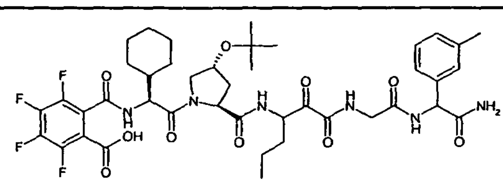
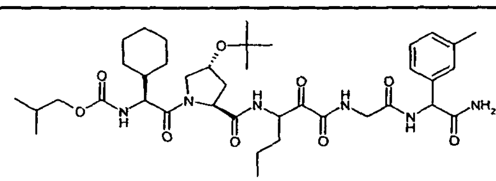
	C
	C
	B
	B
	B
	B
	B
	B

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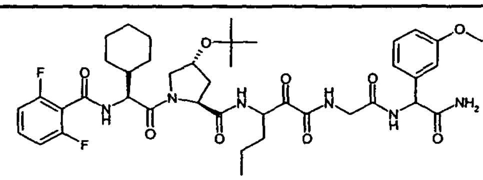
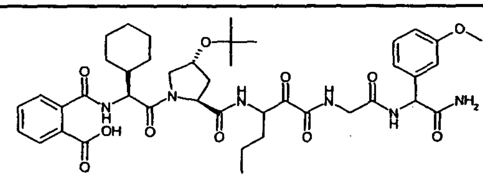
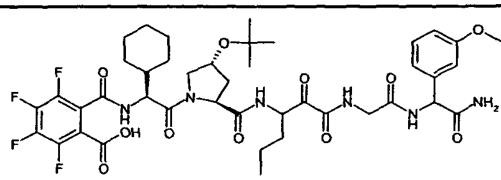
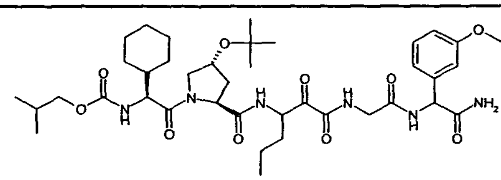
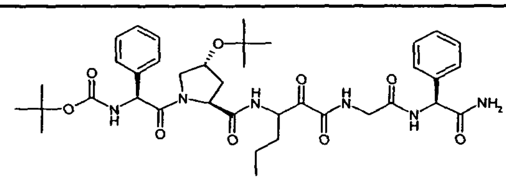
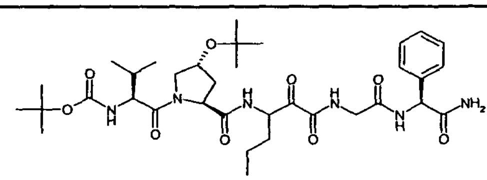
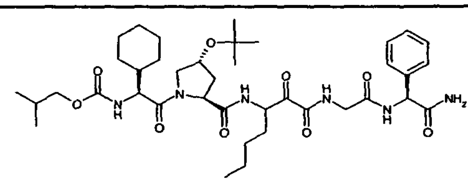
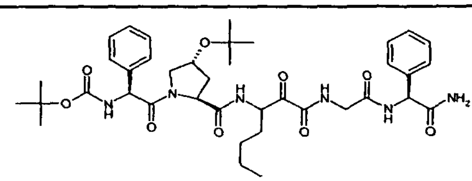
	B
	B
	B
	B
	C
	B
	B
	C

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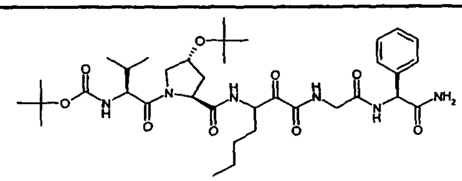
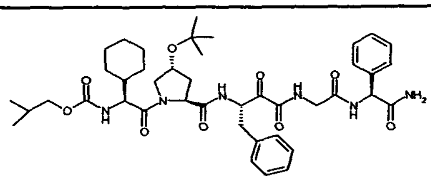
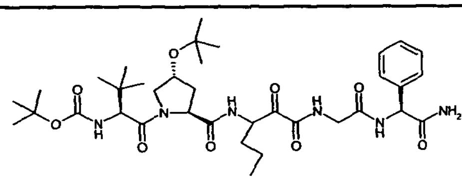
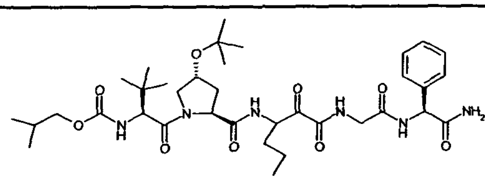
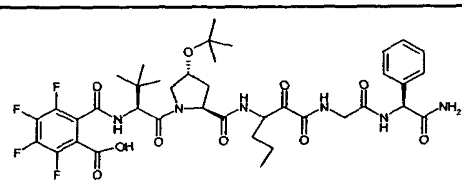
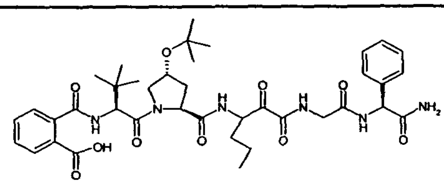
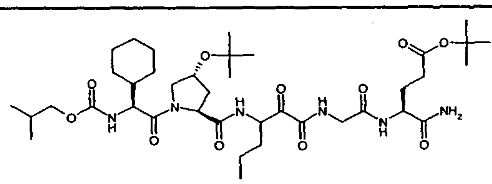
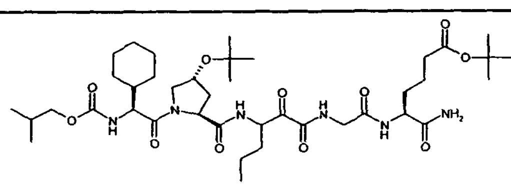
	B
	C
	B
	B
	B
	B
	C
	C

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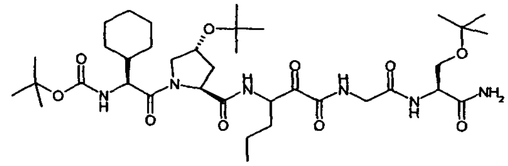
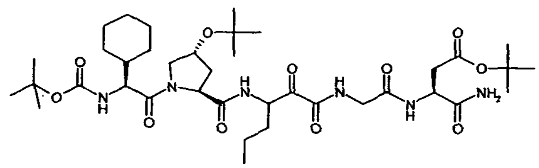
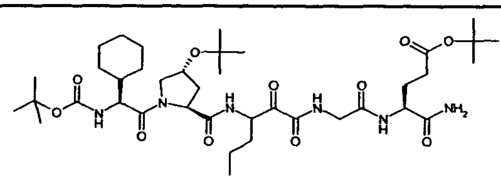
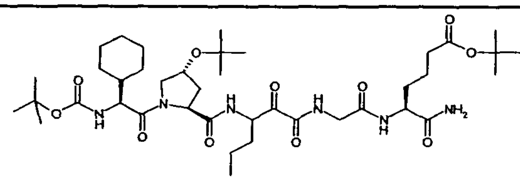
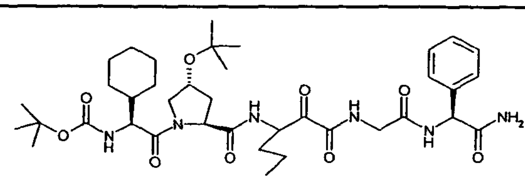
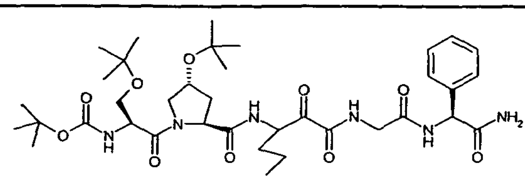
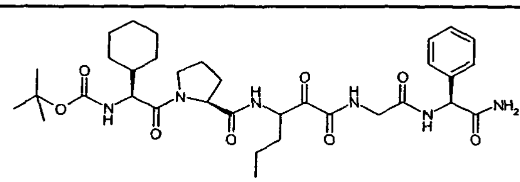
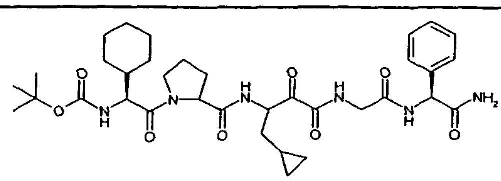
	C
	C
	C
	C
	B
	C
	C
	C

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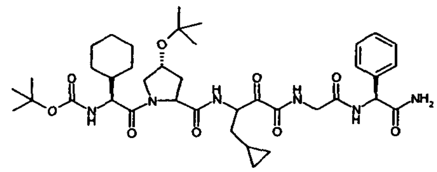
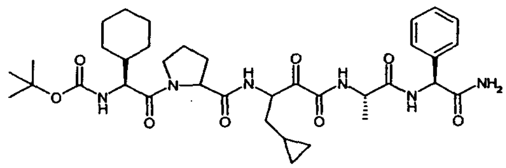
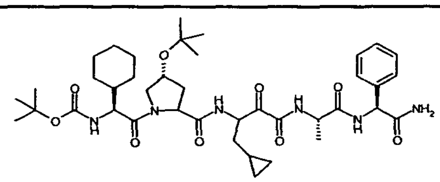
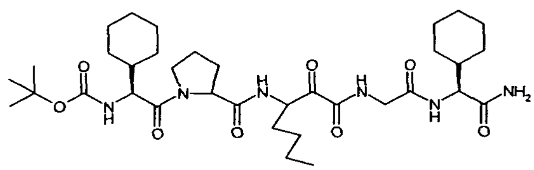
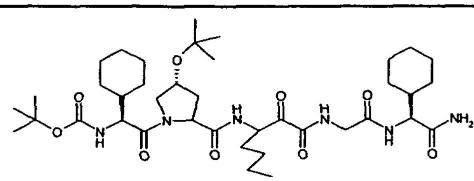
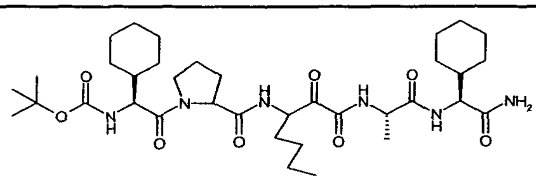
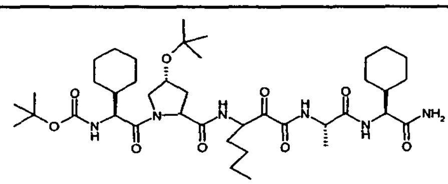
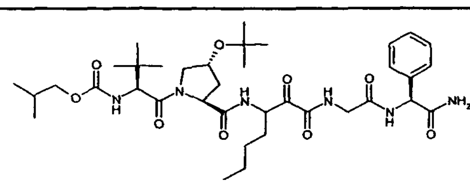
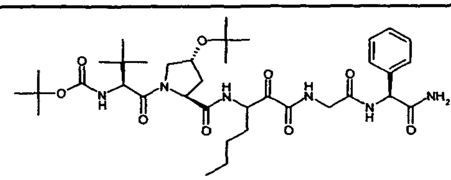
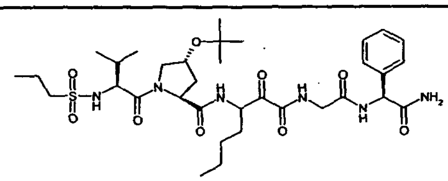
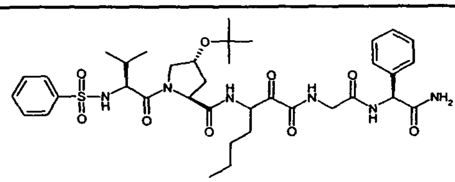
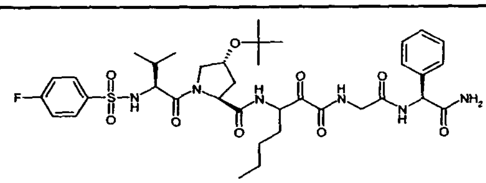
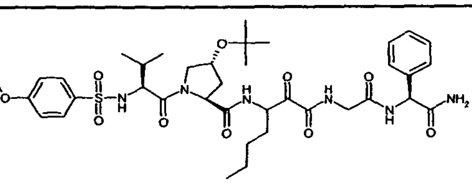
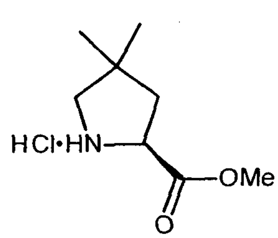
	B
	C
	B
	C
	C
	C
	C
	B

STRUCTURE	Ki* CLASS
	B
	C
	C
	C
	C

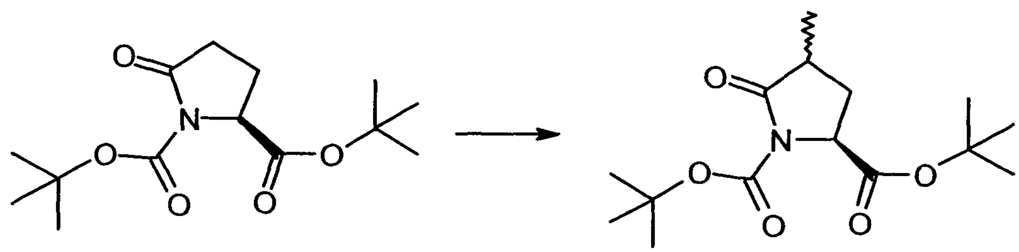
Additional compounds that were prepared and their activity (Ki*) ranges are given in the attached **Tables 4, 5 and 6**. The procedure used to prepare the compounds in **Tables 4, 5** and **6** is outlined below.

I) <u>Synthesis of intermediates for the compounds in Tables 4, 5 and 6:</u>

Example I. Synthesis of 4,4-dimethyl proline methyl ester (H-Pro(4,4-diMe)-OMe)

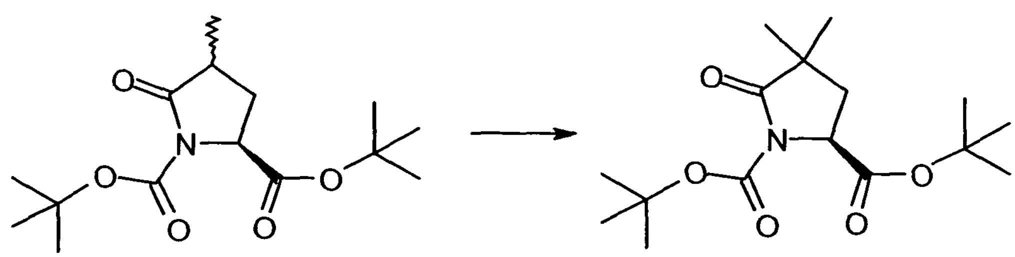


Step 1. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (Boc-PyroGlu(4-methyl)-OtBu):



To a solution of tert-butyl N-tert-butoxycarbonyl-pyroglutamate (11.5 g, 40 mmol) in THF (200 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in THF (42 mL, 42 mmol) dropwise over 5 minutes. After 30 minutes, methyliodide (3.11 mL, 50 mmol) was added. After an additional 2 hours at -78 °C, the cooling bath was removed and 50% saturated aqueous ammonium chloride (200 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed with 1:1 ethylacetate/hexanes to give Boc-PyroGlu(4-methyl)-OtBu (10.6 grams, 35.4 mmol, 88%) as a mixture of isomers (2:1 cis to trans).

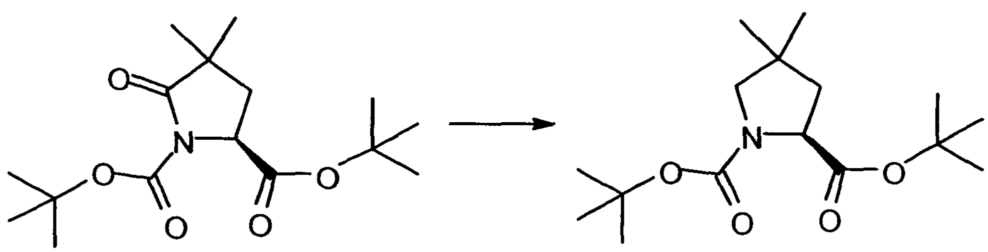
Step 2. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4,4-dimethyl-L-pyroglutamate (Boc-PyroGlu(4,4-dimethyl)-OtBu):



To a solution of tert-butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (1.2 g, 4.0 mmol) in tetrahydrofuran (20 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in tetrahydrofuran (4.4 mL, 4.4 mmol) dropwise over 5 minutes. After 30 minutes, methyliodide (0.33 mL, 5.2 mmol) was added. After an additional 3 hours at -78 °C, the cooling bath was removed and

50% saturated aqueous ammonium chloride (40 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (2 x 50 mL). The combined organic layers were washed with water(2 × 25 mL), saturated sodium bicarbonate (2 × 25 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated to give Boc-PyroGlu(4,4-dimethyl)-OtBu (0.673 g, 54%).

Step 3. Synthesis of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylproline (Boc-Pro(4,4-dimethyl)-OtBu)

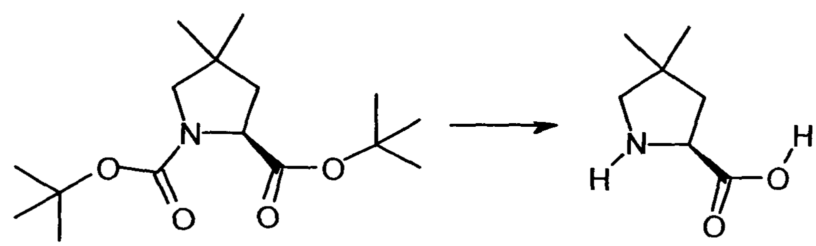


Modification of known procedure: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* **1994**, 35(13), 2053-2056).

To a solution of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylpyroglutamate (2.0 mmol) in tetrahydrofuran (5 mL) stirring at -78 °C, was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (2.4 mL, 2.4 mmol) dropwise over 5 minutes. After 30 minutes, the cooling bath was removed and saturated aqueous sodium bicarbonate (5 mL) was added. The reaction mixture was immersed in an ice/water bath and 30% aqueous hydrogen peroxide (10 drops) was added. The solution was stirred for 20 minutes at 0 °C, then the reaction mixture was concentrated *in vacuo* to remove the tetrahydrofuran. The aqueous solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 40 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in dichloromethane (20 mL) and triethylsilane (310 μL, 2.0 mmol), then cooled to -78 °C and boron trifluoride diethyletherate (270 μL, 2.13 mmol) was added dropwise. Stirring was continued for 30 minutes, at which time additional

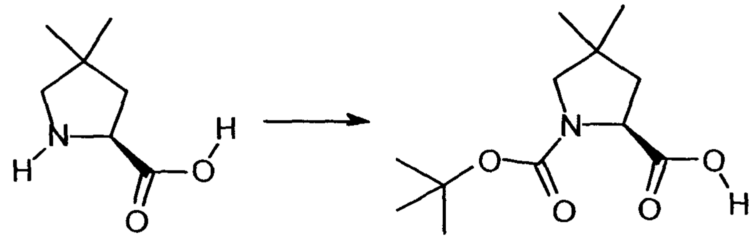
triethylsilane (310 μL, 2.0 mmol) and boron trifluoride diethyletherate (270 μL, 2.13 mmol) were added. After stirring at -78 °C for an additional two hours, the cooling bath was removed and saturated aqueous sodium bicarbonate (4 mL) was added. After 5 minutes the mixture was extracted with dichloromethane (3 x 40 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated to give Boc-Pro(4,4-dimethyl)-OtBu.

Step 4. Synthesis of 4,4-dimethylproline (H-Pro(4,4-dimethyl)-OH):



A solution of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylproline in dichloromethane (5 mL) and trifluoroacetic (5 mL) was stirred at room temperature for five hours. The solution was concentrated, dried under high vacuum and taken to the next step without further purification.

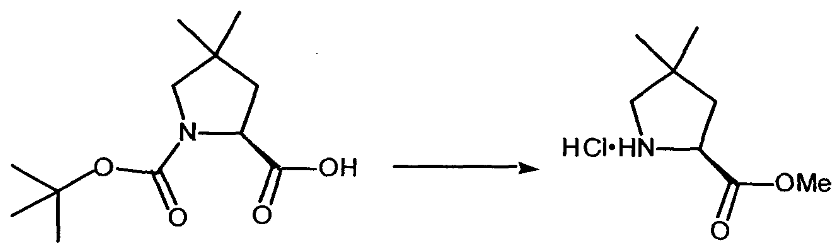
Step 5. Synthesis of N-tert-butoxycarbonyl 4,4-dimethylproline (Boc-Pro(4,4-dimethyl)-OH):



To a solution of 4,4-dimethylproline trifluoroacetic salt (1.5 mmol) in dioxane (7 mL), acetonitrile (12 mL) and diisopropylethylamine (700 μL, 4 mmol) was added a solution of di-tert-butyl-dicarbonate (475 mg, 2.18 mmol) in acetonitrile (5 mL). After stirring for 12 hours at room temperature the solution was concentrated in vacuo, dissolved in saturated aqueous sodium bicarbonate

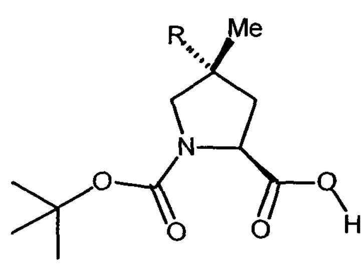
(50 mL) and washed with diethyl ether (3 x 40 mL). The aqueous layer was acidified to pH=3 with citric acid, then extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over sodium sulfate filtered and concentrated.

Step 6. Synthesis of 4,4-dimethylproline methylester hydrochloride salt (HCl•H-Pro(4,4-dimethyl)-OMe):



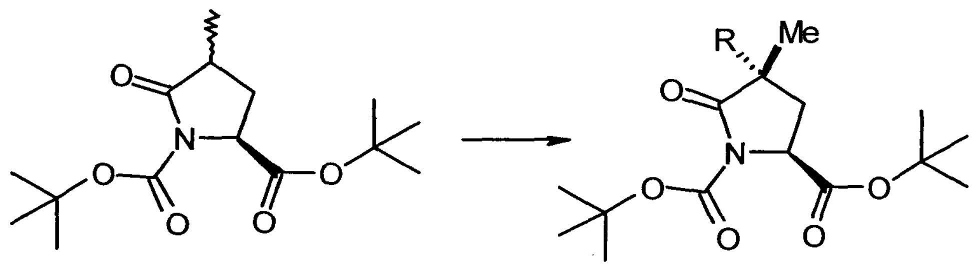
To a solution of Boc-Pro(4,4-diMe)-OH (0.5 g, 2.06 mmol) in anhydrous methanol (8 ml) was added dropwise thionylchloride (448 l, 6.18 mmol) and the reaction was stirred for six hours at room temperature. The reaction mixture was concentrated to an amorphous solid (377 mg, 95%).

Example II. General procedure for the synthesis of N-tertbutoxycarbonyl-4-alkyl-4-methyl proline:



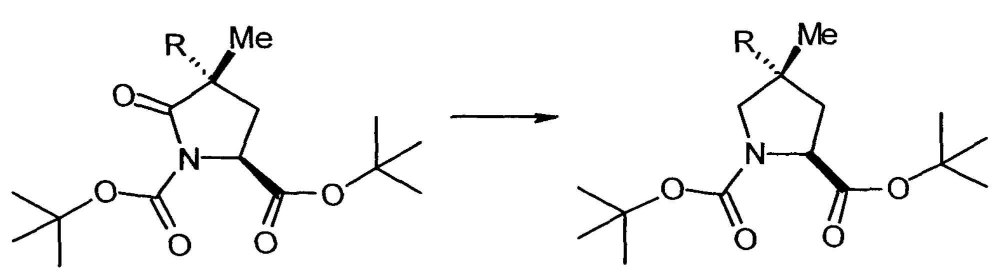
Compounds where R group is allyl and benzyl were synthesized following steps 1-4 below:

Step 1. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4-alkyl-4-methyl-L-pyroglutamate:



To a solution of tert-butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (10.2 g, mmol) (see Example I, step 1) in tetrahydrofuran (170 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in tetrahydrofuran (37.5 mL, 37.5 mmol) dropwise over 5 minutes. After 40 minutes, alkyl halide (61.4 mmol) was added. After an additional 3 hours at -78 °C, the cooling bath was removed and 50% saturated aqueous ammonium chloride (200 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (2 x 200 mL). The combined organic layers were diluted with hexanes (150 mL) and washed with saturated sodium bicarbonate (100 mL), water (2 x 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was flash chromatographed using 20% ethylacetate in hexanes to give the pure tert-Butyl N-tert-butoxycarbonyl-4-alkyl-4-methyl-L-pyroglutamate.

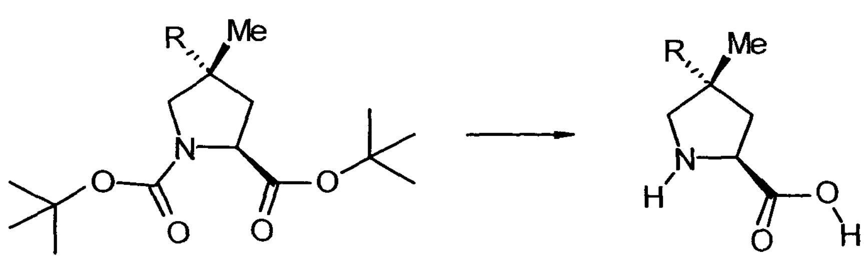
Step 2. Synthesis of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline:



Modification of known procedure: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* (1994) 35(13), 2053-2056).

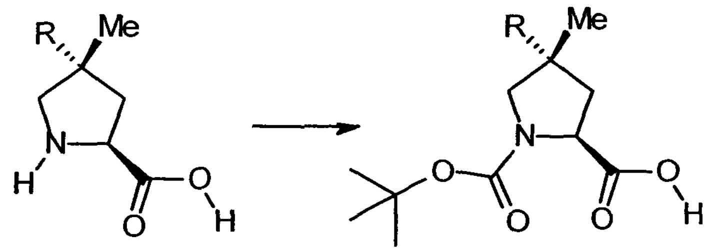
To a solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylpyroglutamate (16.6 mmol) in tetrahydrofuran (40 mL) stirring at -78 °C, was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (20 mL, 20 mmol) dropwise over 10 minutes. After 120 minutes, the cooling bath was allowed to warm to –25 °C at which point saturated aqueous sodium bicarbonate (40 mL) was added. The reaction mixture was immersed in an ice/water bath and 30% aqueous hydrogen peroxide (4 mL) was added. The solution was stirred for 10 minutes at 0 °C, then the reaction mixture was concentrated in vacuo to remove the tetrahydrofuran. The aqueous solution was diluted with water (300 mL) and extracted with dichloromethane (3 x 200 mL). The organic layers were dried (sodium sulfate), filtered and concentrated. The residue was dissolved in dichloromethane (100 mL) and triethylsilane (2.6 mL, mmol), then cooled to -78 °C and boron trifluoride diethyletherate (2.2 mL, mmol) was added dropwise. Stirring was continued for 1 hour, at which time additional triethylsilane (2.6 mL, mmol) and boron trifluoride diethyletherate (2.2 mL, mmol) were added. After stirring at -78 °C for an additional 4 hours, the cooling bath was removed and saturated aqueous sodium bicarbonate (30 mL) and water (150 mL) were added. After 5 minutes the mixture was extracted with dichloromethane (3 x 200 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated.

<u>Step 3. Synthesis 4-alkyl-4-methylproline:</u>



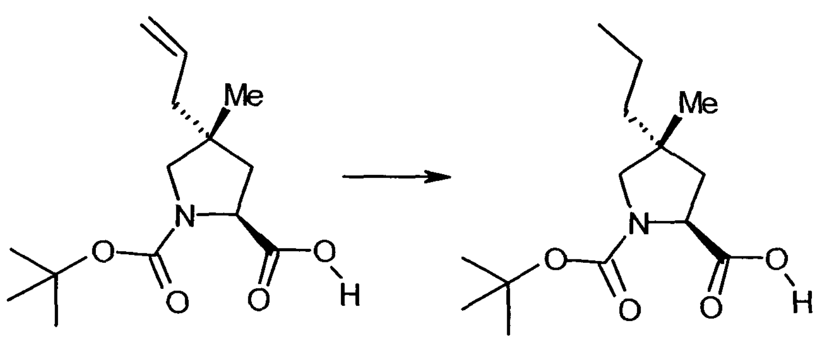
A solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline in dichloromethane (5 mL) and trifluoroacetic (5 mL) was stirred at room temperature for 5 hours. Toluene was added and the solution was concentrated and then dried under high vacuum.

Step 4. Synthesis of N-tert-butoxycarbonyl 4-alkyl-4-methylproline:



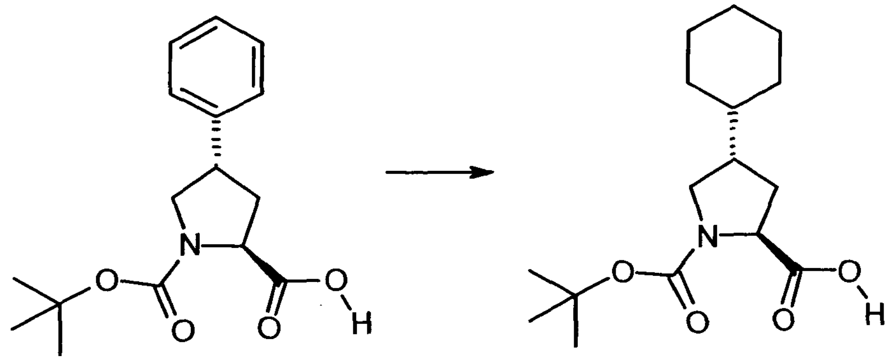
To a solution of 4-alkyl-4-methylproline trifluoroacetic salt (1.5 mmol) in dioxane (7 mL), acetonitrile (12 mL) and diisopropylethylamine (700 μL, 4 mmol) was added a solution of di-tert-butyl-dicarbonate (475 mg, 2.18 mmol) in acetonitrile(5 mL). After stirring for 12 hours at room temperature the solution was concentrated in vacuo, dissolved in saturated aqueous sodium bicarbonate (50 mL) and washed with diethyl ether (3 x 40 mL). The aqueous layer was acidified to pH=3 with 1N hydrochloric acid, then extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography using 1:1 ethylacetate/hexanes with 1% acetic acid.

Example III. Synthesis of N-tert-butoxycarbonyl 4-propyl-4-methylproline:



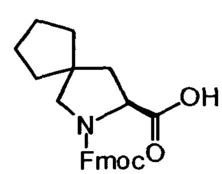
A solution of N-tertbutoxycarbonyl-4-allyl-4-methylproline (400 mg, 1.48 mmol) (see Example II Step 4) and 10% Pd on carbon (400 mg) in methanol (20 mL) was hydrogenated at 50 psi for 4 hours. The mixture was filtered and concentrated.

Example IV. Synthesis of Boc-4-cyclohexylproline:

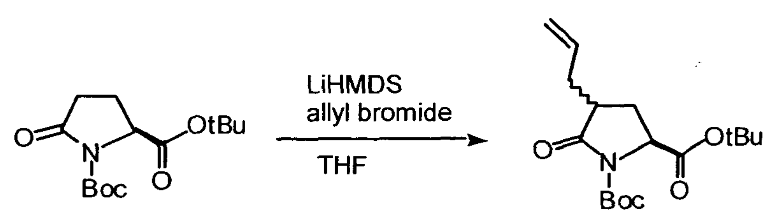


A solution of the commercially available Boc-4-phenylproline (750 mg) and 5% Rh on carbon (750 mg) in methanol (15 mL) was hydrogenated at 50 psi for 24 hours. The mixture was filtered and concentrated to give 730 mg of product.

Example V: Preparation of Fluorenylmethoxycarbonyl-Pro(4-spirocyclopentane)-carboxylic acid :



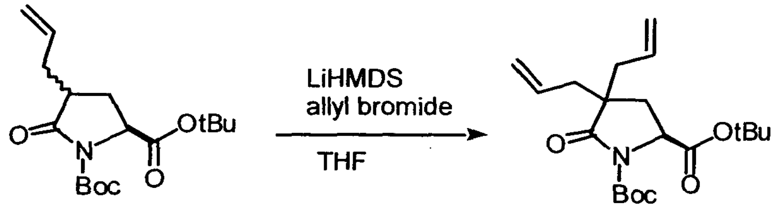
Step 1. Synthesis of Boc-pyroglutamic(4-allyl)-tert-butylester :



To a cooled (-78 °C) solution of the commercially available N -Boc-tert-butyl pyroglutamate (10 g, 35.1 mmol) in THF (175 ml) was added lithium hexamethyldisilazide (36.8 mL, 36.8 mmol) over five minutes. Stirring continued for thirty minutes. A solution of allyl bromide (6.1 ml, 70.2 mmol) in THF (39 mL) was added dropwise to the first solution. After two hours at -78 °C, the reaction was quenched by the slow addition of saturated ammonium chloride (50 mL) solution. The reaction mixture was then diluted with ethylacetate and the layers were separated. The organic layer dried over sodium sulfate and concentrated.

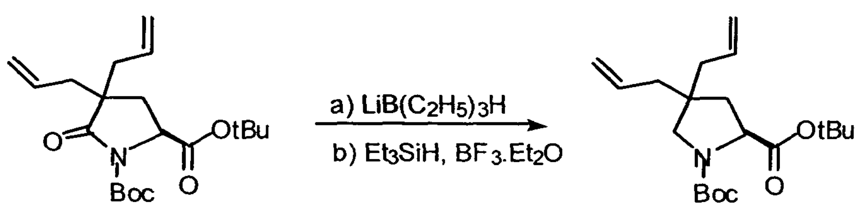
Flash column chromatography carried out in 2:8 ethylacetate: hexanes afforded the product (6 g, 53%). NMR δ ppm (CDCl3): 5.7 (m, 1H), 5.1 (dd, 2H), 4.4 (m, 1H), 2.6 (m, 2H), 2.4 (m, 1H), 1.8-2.2 (m, 1H), 1.45 (s, 9H), 1.4 (s, 9H).

Step 2. Synthesis of N-Boc-pyroglutamic(4,4-diallyl)-tert-butylester:



N-Boc-pyroglutamic(4-allyl)-tert-butylester obtained in the Step 1 above (2.68 g, 8.24 mmol) was subjected to a second alkylation with allyl bromide under similar conditions. Flash chromatography in 15:85 ethylacetate: hexanes provided 2.13 g product (71%) as a clear oil.

Step 3. Synthesis of Boc-Pro(4,4-diallyl)-tert-butylester:

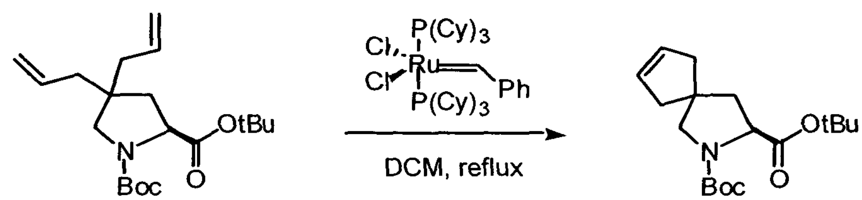


Part a: To a cooled (-78 °C) solution of Boc-PyroGlu(4,4-diallyl)-tert-butylester (2.13 g, 5.83 mmol) in tetrahydrofuran (14 ml) was added lithium triethylborohydride (1M in tetrahydrofuran, 7.29 ml, 7.29 mmol) over five minutes. After two hours at -78 °C, the reaction was warmed-up to 0 °C and quenched by the slow addition of saturated sodium bicarbonate solution (20 ml) and 30% hydrogen peroxide (20 drops). Stirring continued for 20 minutes. The tetrahydrofuran was removed under reduced pressure and the remaining thick white residue was diluted with water (80 ml) and extracted three times with dichloromethane. The organic layer was dried, filtered and concentrated and taken to the next step without further purification.

Part b): To the product obtained in part (a) in dichloromethane (14 ml) was added triethylsilane (931 μl, 5.83 mmol) followed by boron trifluoride diethyl

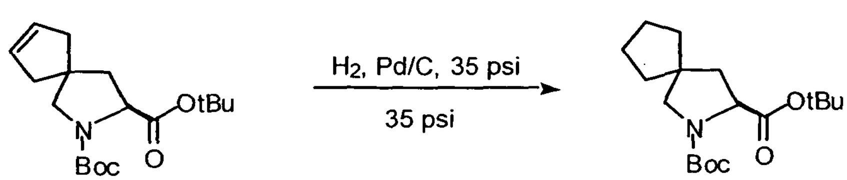
etherate (776 μl, 6.12 mmol). After thirty minutes more triethylsilane (931 μl, 5.83 mmol) and boron trifluoride diethyl etherate etherate (776 μl, 6.12 mmol) were added and the reaction was stirred at -78 °C for three hours at which time the reaction was quenched by the slow addition of saturated sodium bicarbonate solution and water. The reaction mixture was extracted with dichloromethane and the organic layer was dried, filtered and concentrated. Flash column chromatography in 15% ethylacetate in hexanes afforded 1.07 colorless oil (57%). NMR δ ppm (CDCl3): 5.7-5.8 (m, 2H), 5.1 (m, 4H), 4.1-4.2 (2 dd's, 1H rotamers), 3.5-3.3 (dd, 1H) and 3.2 (dd, 1H) rotamers, 2.2-2.0 (m, 5H), 1.7(m, 1H), 1.46 (s, 9H), 1.43 (s, 9H).

<u>Step 4. Synthesis of Boc-Pro(4-spirocyclopentene)-tert-butylester:</u>



To Boc-Pro(4,4-diallyl)-tert-butylester (1.07 g, 3.31 mmol) in dichloromethane (66 ml) was added 5% Bis(tricyclohexylphosphin)benzylidene ruthenium IV dichloride (Grubbs catalyst) and the mixture was heated at reflux for 1.5 hours. The reaction mixture was concentrated and the remaining residue was purified by flash column chromatography in 15% ethylacetate in hexanes. A yellow oil was obtained (0.57 g, 53%). NMR δ ppm (CDCl3): 5.56 (bs, 2H), 4.2 and 4.1 (t, 1H, rotamers), 3.2-3.5 (m, 2H), 2.2-2.5 (m, 5H), 1.9 (dd, 1H) 1.47 and 1.46 (2 s's, 9H, rotamers), 1.45 and 1.44 (2 s's, 9H, rotamers).

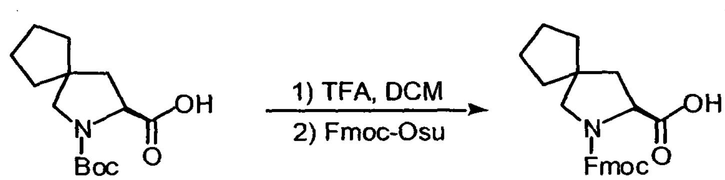
<u>Step 5. Synthesis of Boc-Pro(4-spirocyclopentane)-tert-butylester:</u>



A solution of Boc-Pro(4-spirocyclopentene)-tert-butylester (1.12 g) in methanol (18 ml), water (4 ml) and acetic acid (4 ml) was placed in the Parr

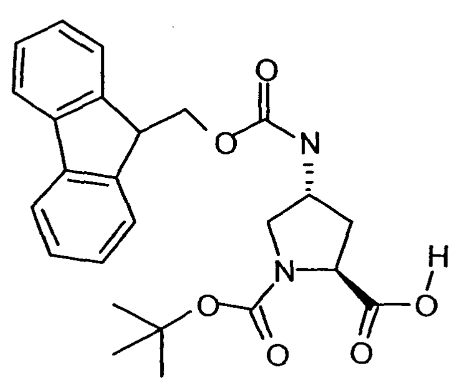
shaker and was hydrogenated for three hours at 35 psi in the presence of 10% palladium on carbon (300 mg). The catalyst was filtered off and the filtrate was concentrated to a colorless oil (1.26 g). NMR δ ppm (CDCl3): 4.1 and 4.2 (t, 1H, rotamers, 3.4 (d, 1H), 3.2 (d, 1H), 2.1 (m, 1H), 1.9 (m, 1H), 1.6-1.7 (m, 10H), 1.5 (3 s's, 18H, rotamers).

Step 6. Synthesis of Fmoc-Pro(4-spirocyclopentane)-carboxylic acid:

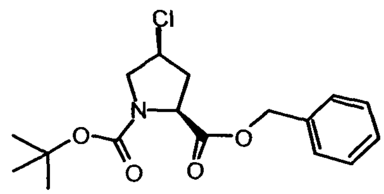


The Boc-Pro(4-spirocyclopentane)-tert-butylester (1.26, 3.9 mmol) was treated with dichloromethane (10 ml) and trifluoroacetic acid (15 ml) for three hours. The reaction mixture was concentrated and the yellow oil obtained was dissolved in water (6 ml). Fluorenylmethyl succinyl carbonate (1.45 g, 4.3 mmol) dissolved in dioxane (6 ml) was added portionwise followed by the addition of potassium carbonate (2.16 g, 15.6 mmol). The reaction was stirred for 18 hours and concentrated. The remaining residue was diluted with the saturated sodium bicarbonate solution (10 mL) and washed with diethylether (3 × 10 ml). The aqueous layer was then acidified to pH ~ 1 with 1N sodium bisulfate solution and extracted with ethylacetate. The organic layer was dried over sodium sulfate, filtered and concentrated to a beige foam (1.3 g, 100%).

Example VI. Synthesis of Boc-Pro(4t-NH(Fmoc))-OH:

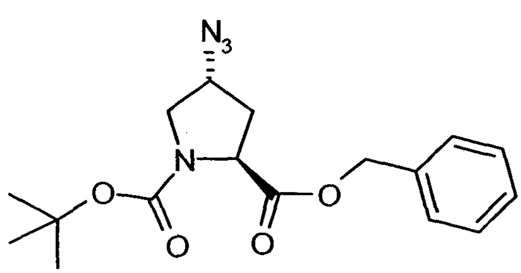


Step 1. Synthesis of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester:



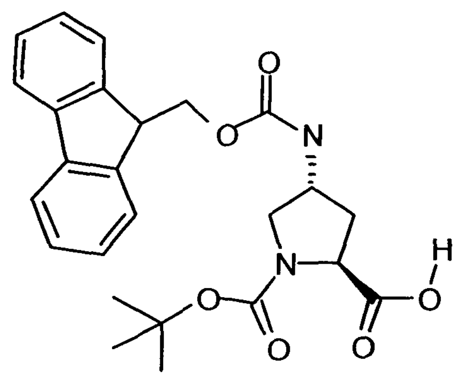
A mixture of the commercially available N -tert-butoxycarbonyl-trans-4-hydroxy-proline (8.79 g, 38 mmol), potassium carbonate (13.0 g, 94 mmol), benzyl bromide (4.5 ml, 38 mmol) and dimethylformamide (150 mL) was stirred for 18 h. Addition of ethyl acetate (100 mL) was followed by filtration. The white cloudy filtrate was clarified by the addition of 1M HCl (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), dried (sodium sulfate), filtered and concentrated. Toluene was added to the crude benzyl ester, and the solution was filtered and reconcentrated. Dichloromethane (70 mL) and carbon tetrachloride (70 mL) was added, followed by triphenylphosphine (21.11 g, 80 mmol). The reaction mixture was stirred for 10 h, quenched with ethanol (7 mL) and stirred for 5 more h. The solution was concentrated to approx. 100 ml, then dichloromethane (40 mL) was added, followed by the addition of ether (200 mL) while stirring. The solution was cooled for 4 h, filtered and concentrated to give a yellow-brown oil which was purified by flash chromatography using ether/hexane/dichloromethane 2:2:1 to give the title compound (9.13 g, 26.9 mmol, 71%) as a white solid.

Step 2. Synthesis of N^{α}-tert-butoxycarbonyl-trans-4-azido-L-proline benzyl ester:



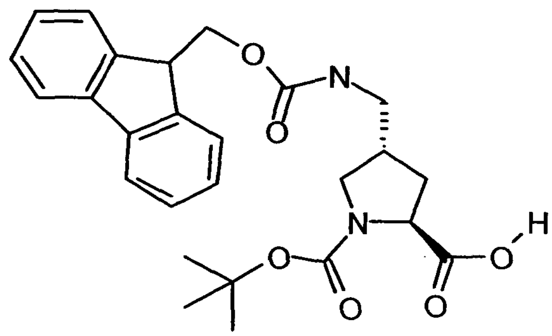
A solution of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester (9.0 g, 26.5 mmol) and sodium azide (7.36 g, 113 mmol) in dimethylformamide (270 mL) was heated at 75°C for 2 days. Water (100 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 50 mL), dried (sodium sulfate), filtered and concentrated. The oil was purified by flash chromatography using ethyl acetate/hexanes 1:1 to give the title compound (8.59 g, 24.8 mmol, 94%).

Step 3. Synthesis of Boc-Pro(4t-NH(Fmoc))-OH:

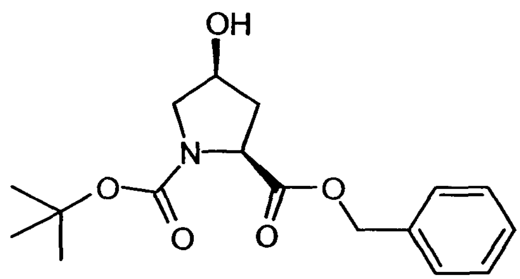


A mixture of N-α-t-butoxycarbonyl-trans-4-azido-L-proline benzyl ester (8.59 g, 24.8 mmol) and 10% palladium on carbon (900 mg) in ethanol (500 mL) was hydrogenated at 50 psi for 14 h using a Parr hydrogenation apparatus. The mixture was filtered, concentrated, dissolved in methanol (60 mL), refiltered and concentrated to give a colorless oil. The oil was dissolved in water (53 mL) containing sodium carbonate (5.31 g, 50.1 mmol) and a solution of fluorenylmethyl succinyl carbonate (8.37 g, 29.8 mmol) in dioxane (60 mL) was added over 40 min. The reaction mixture was stirred at room temperature for 17 h, then concentrated to remove the dioxane and diluted with water (200 mL). The solution was washed with ether (3 x 100 mL). The pH of the aqueous solution was adjusted to 2 by the addition of citric acid (caution! foaming!) and water (100 mL). The mixture was extracted with dichloromethane (400 mL, 100 mL, 100 mL) and the combined organic layers were dried (sodium sulfate), filtered and concentrated to give the title compound.

Example VII. Synthesis of N-t-butoxycarbonyl-4-trans-(N-fluorenylmethyloxycarbonyl aminomethyl)-L-proline (Boc-Pro(4t-MeNHFmoc)-OH):



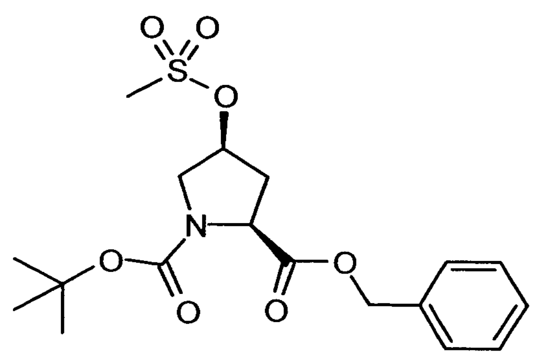
Step 1. Synthesis tert-butoxycarbonyl cis-4-hydroxy-L-proline benzyl ester (Boc-Pro(4-cis-OH)-OBn):



To a mixture of cis-hydroxy-L-proline (5 g, 38.1 mmol) in benzene (45 mL) and benzyl alcohol (45 mL) was added p-toluenesulfonic acid monohydrate (7.6 g, 40.0 mmol). The reaction mixture was heated at 125°C for 20 h while water (2ml) was removed using a Dean-Stark trap. The solution was filtered while still hot, and then ether (150 ml) was added. The solution was allowed to cool for three h at room temperature, then three h at 4 °C. The resulting solid was collected, washed with ether (100 mL) and dried in vacuo for 1 h to give 13.5 grams of white solid. The solid was dissolved in dioxane (40 mL) and diisopropylethylamine (7.6 mL), and then di-tert-butyl-dicarbonate (10 g, 45.8 mmol) was added over 5 min while using an ice bath to maintain a constant reaction temperature. After 10 h at room temperature the reaction mixture was poured into cold water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL) and saturated aqueous sodium chloride (50 mL),

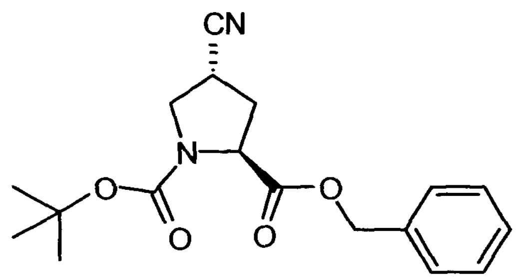
dried (sodium sulfate), filtered and concentrated. The crude product was purified by flash chromatography using 40-60% ethyl acetate in hexanes to give the title compound (10.04 g, 31.24 mmol, 82%).

Step 2. Synthesis of N-t-butoxycarbonyl cis-4-mesyloxy-L-proline benzyl ester (Boc-Pro(4-cis-OMs)-OBn):



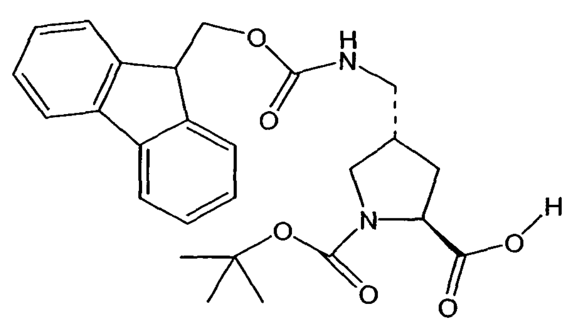
To a solution of Boc-Pro(4-cis-OH)-OBn (8.45 g, 26.3 mmol) in pyridine (65 mL) at 0°C, was added methanesulfonyl chloride (3.4 mL, 44 mmol) dropwise over 7 min. The reaction mixture was allowed to warm to room temperature over 2 h, then stirred overnight. A solution of 10% water in pyridine (20 mL) was added over 15 min and the reaction mixture was concentrated. The residue was dissolved in water and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water (2 x 50 mL) saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium chloride (50 mL), dried (sodium sulfate), filtered and concentrated. The resulting residue was dissolved in toluene (100 mL) and concentrated to remove traces of pyridine. The residue was dried in vacuo for 30 min to afford the title compound (10.7 g, 102%), then used in the next step without purification.

Step 3. N-t-butoxycarbonyl-trans-4R-cyano-L-proline benzylester (Boc-Pro(4-trans-CN)-OBn):



A solution of Boc-Pro(4-cis-OMs)-OBn (10.7 g, 26.3 mmol) and tetrabutylammonium cyanide (15.0 g, 56 mmol) in dimethylformamide (100 mL) was heated in an oil bath at 55°C for 28 h. After cooling, water (150 mL) was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL) and saturated aqueous sodium chloride (100 mL), dried (sodium sulfate), filtered and concentrated. The resulting residue was purified by flash chromatography (1:1 ether/hexanes) and then recrystallized from ethyl acetate/hexanes to provide the title compound (2.40 g, 7.26 mmol, 28%).

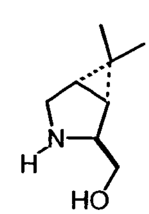
Step 4. N-t-butoxycarbonyl-4-trans-(N-fluorenylmethyloxycarbonyl aminomethyl)-L-proline (Boc-Pro(4t-MeNHFmoc)-OH) :



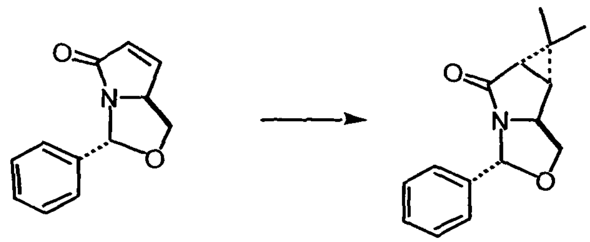
A mixture of the compound of Step 3 above (2.31 g, 7 mmol), water (10 mL), methanol (85 mL) and 10% palladium on carbon (700 mg) was hydrogenated at 50 psi for 11 h using a Parr hydrogenation apparatus. The mixture was filtered and concentrated. Water (15 mL) and sodium carbonate (1.5 g, 14.2 mmol) was added to the residue. A solution of fluorenylmethyl succinyl carbonate (2.36 g, 7.0 mmol) in dioxane (17 mL) was added over 5 min and stirring was continued for 28

h at room temperature. The reaction was concentrated in vacuo to a 15 mL volume, and water (100 mL) was added. The solution was washed with ether (3 x 75 mL). The pH of the aqueous solution was adjusted to 2 by the addition of citric acid (approx. 20 g, caution! foaming!) and water (100 mL). The mixture was extracted with dichloromethane (4 x 100 mL), and the combined organic layers were dried (sodium sulfate), filtered and concentrated. The crude product contained a major impurity which necessitated a three step purification. The crude product was dissolved in dichloromethane (50 mL) and trifluoroacetic acid (50 mL) and stirred for 5 h before being concentrated. The residue was purified by preparatory reverse-phase HPLC. The pure 4-(N-fluorenylmethyloxycarbonyl aminomethyl)proline trifluoroacetate salt (1.887 g, 3.93 mmol) was dissolved in dioxane (10 mL), acetonitrile (20 mL) and diisopropylethylamine (1.4 mL, 8 mmol). To the reaction mixture was added a solution of di-tert-butyldicarbonate (1.1g, 5 mmol) in dioxane (5 mL). After stirring for 18 h, the pH of the solution was adjusted to 2 by the addition of citric acid (caution: foaming!) and water (100 mL). The mixture was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (100 mL), dried (sodium sulfate), filtered and concentrated. The crude product was dissolved in saturated aqueous sodium bicarbonate(100 mL) and washed with ether (3 x 75 mL). The aqueous layer was adjusted to pH = 3 by the addition of citric acid, then extracted with dichloromethane (4 x 100 mL). The combined organic layers were dried (sodium sulfate), filtered and concentrated to the title compound (1.373 g, 2.94 mmol, 42%).

Example VIII. Synthesis of 3,4-isopropylideneprolinol:

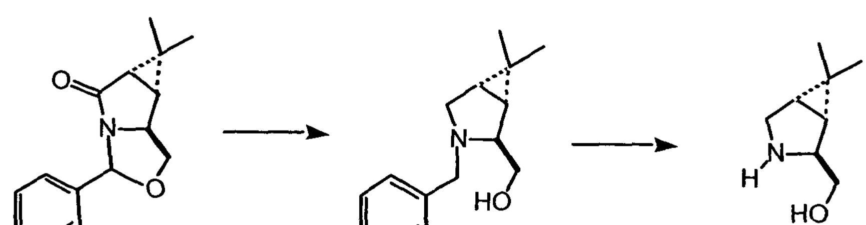


Step I. Cyclopropanation reaction (*Tetrahedron Lett.* 1993, 34(16), 2691 and 2695):



To a stirring solution of isopropyltriphenyl- phosphonium iodide (4.14 g, 9.58 mmol) in tetrahydrofuran (60 mL) at 0 °C, was added n-butyllithium (1.6 M in hexanes, 5.64 mL, 9.02 mmol) over 5 min. After 30 min, a solution of enamide ((5R, 7S)-5-phenyl-5,6,7,7a-tetrahydro-6-oxapyrrolizin-3-one) (1.206 grams, 6.0 mmol) (see *J. Org. Chem.* 1999, 64(2), 547 for the synthesis of the enamide starting material) in tetrahydrofuran (40 mL) was added over 10 min. After an additional 10 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 hours. The reaction was poured into water (400 mL) and extracted with diethyl ether (400 mL) and ethylacetate (2 x 400 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated to give the desired crude product. The residue was purified by flash chromatography eluting with 3:5:2 ethylacetate/hexanes/methylene chloride to give pure cyclopropanated product (750 mg, 3.08 mmol, 51%).

Step 2. Synthesis of 3,4-isopropylideneprolinol P[3,4-(diMe-cyclopropyl)]-alcohol) (*J. Org. Chem.* (1999) 64(2), 330):

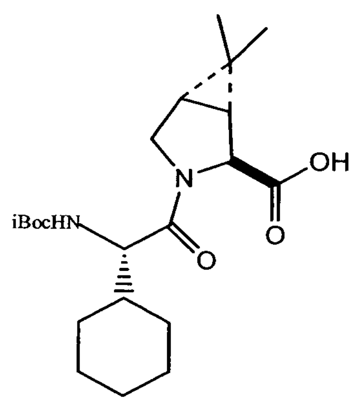


a b c

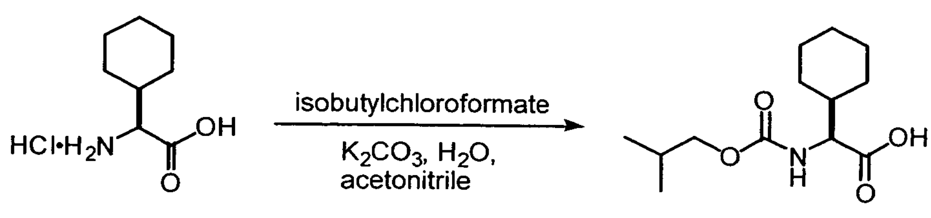
A mixture of the product obtained in step 1 above (1.23 grams, 5.06 mmol) and lithium aluminum hydride (1.0 M in THF, 15 mL, 15 mmol) was heated at reflux for 5 hours. After cooling to 0 °C, the remaining aluminum hydride was carefully quenched by the dropwise addition of saturated aqueous sodium sulfate

(1.5 mL) over 15 min. The mixture was diluted with ethylacetate (40 mL) and then filtered through celite. The filtrate was dried with sodium sulfate, filtered and concentrated to give crude N-benzyl aminoalcohol (1.25 grams), which was carried on to the next step without further purification. A solution of crude N-benzyl aminoalcohol (1.25 grams, 5.06 mmol) in 1:1 acetic acid/ethylacetate (30 mL) with 10% Pd/C (1 gram) was hydrogenated at 50 psi for 16 hours using a Parr hydrogenation apparatus. The reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in water (30 mL) and the pH was adjusted to 13 with 50% NaOH. The mixture was extracted with ether (3 x 60 mL). The combined extract was dried with sodium sulfate, filtered and concentrated to give crude aminoalcohol (485 mg, 3.43 mmol). This material was taken to the next step without further purification.

Example IX. Synthesis of iBoc-G(Chx)-Pro(3,4-isopropylidene)- carboxylic acid :



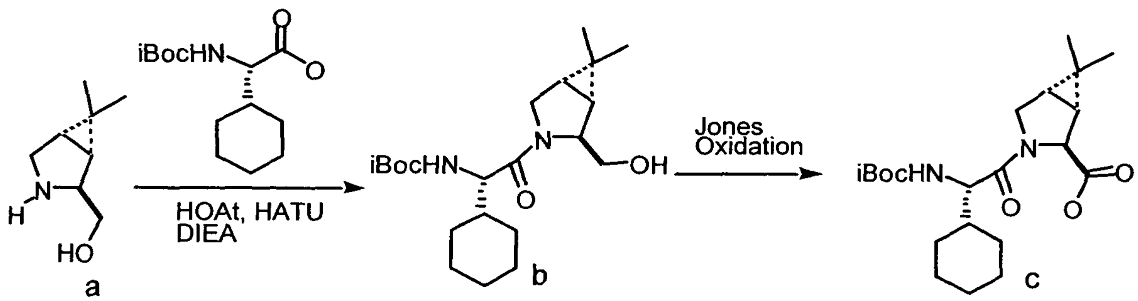
Step 1. Synthesis of isobutyloxycarbonyl- cyclohexylglycine (iBoc-G(Chx)-OH):



To a solution of the commercially available cyclohexylglycine hydrochloride (15 g, 77.4 mmol) in acetonitrile (320 ml) and water (320 ml) was added potassium carbonate. Isobutylchloroformate (11.1 ml, 85.1 mmol) was added to the clear solution over 15 minutes and the reaction was stirred for 17 hours. The

acetonitrile was removed under reduced pressure and the remaining aqueous layer was extracted twice with ether (100 ml). The aqueous layer was then acidified to pH 1 with 6N hydrochloric acid and extracted with dichloromethane (3 × 300 ml). The organic layer was dried over sodium sulfate, filtered and concentrated to yield 18.64 g (94%) product as a white solid.

Step 2. Synthesis of isobutyloxycarbonyl-cyclohexylglycyl-3,4-isopropylideneproline (iBoc-G(Chx)- P[3,4-(diMe-cyclopropyl)]-OH):



a) Coupling step

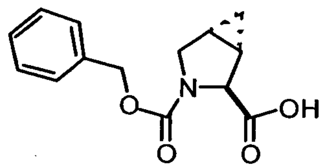
To a solution of iBoc-G(Chx)-OH (890 mg, 3.45 mmol) in acetonitrile (20 mL) was added HATU (1.33 g, 3.5 mmol), HOAt (476 mg, 3.5 grams) and then diisopropylethylamine (2.5 mL, 14 mmol). After a 2 minutes, 3,4-isopropylideneprolinol (485 mg, 3.43 mmol) was added and the reaction mixture was stirred overnight. Addition of saturated aqueous sodium bicarbonate was followed by extraction with ether and ethylacetate. The combined organic layers were dried, filtered and concentrated. The residue was purified by flash chromatography eluting with 1:1 ethylacetate/hexanes to give pure dipeptide alcohol iBoc-G(Chx)-3,4-isopropylideneprolinol (870 mg, 2.3 mmol, 67%)

b) Jones oxidation step

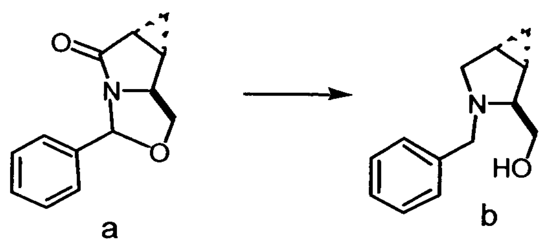
To a solution of dipeptide alcohol iBoc-G(Chx)-3,4-isopropylideneprolinol (100 mg, 0.26 mmol) in acetone (2 mL) stirring at 0 °C was added Jones reagent (300 μL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to a total volume of 50 mL.] After stirring at 0 °C for 3 hours, isopropanol (500 μL) was added and stirring continued for an additional 10 minutes. The reaction mixture

was diluted with water (20 mL) and extracted with ethylacetate (3 x 70 mL). The combined organic layers were dried, filtered and concentrated to give the dipeptide iBoc-G(Chx)-3,4-isopropylideneproline (100 mg, 0.25 mmol, 96%).

Example X. Synthesis of N-Cbz-3,4-methanoproline:

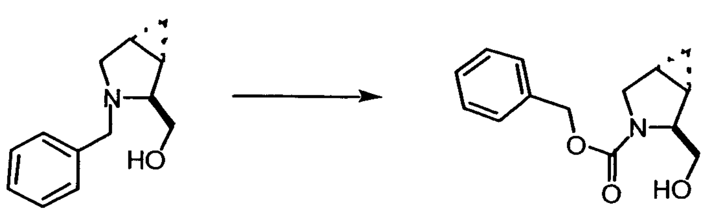


Step 1. Synthesis of N-benzyl-3,4-methanoprolinol:



A mixture of the benzylidene starting material (J. Org. Chem. 1999, 64(2), 547) (4.6 grams, 21.4 mmol) and lithium aluminum hydride (1.0 M in THF, 64 mL, 64 mmol) was heated at reflux for 5 hours. After cooling to 0 °C, the remaining aluminum hydride was carefully quenched by the dropwise addition of saturated aqueous sodium sulfate (5 mL) over 15 min. The mixture was diluted with ethylacetate (200 mL) and then filtered through celite. The filtrate was dried with sodium sulfate, filtered and concentrated to give crude N-benzyl aminoalcohol (3.45 grams), which was carried on to the next step without further purification.

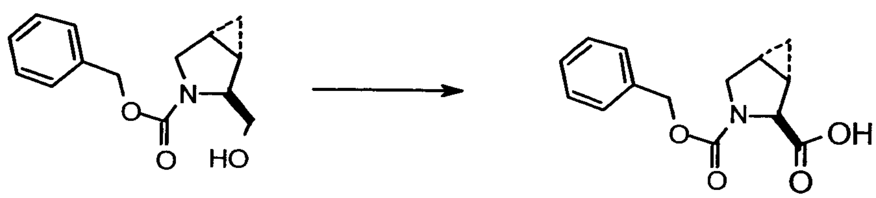
Step 2. Synthesis of N-benzyloxycarbonyl-3,4-methanoprolinol (CBz-P(3,4-CH2)-ol) :



A solution of crude N-benzyl aminoalcohol (3 grams, 14.76 mmol) in methanol (120 mL) and concentrated HCl (1.5 mL) with 10% Pd/C (300 mg) was

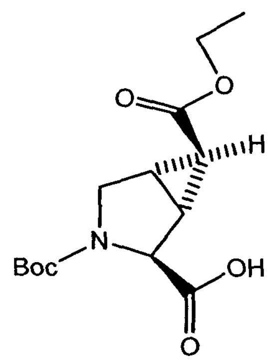
hydrogenated at 50 psi for 16 hours. The reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in water/dioxane (100 mL) and diisopropylethylamine (3.2 mL) was added. Benzyl chloroformate (2.76 mL, 16.2 mmol) was added and the reaction was stirred overnight. The reaction mixture was concentrated, dissolved in 1M HCl (100 mL) and extracted with ethylacetate (3 x 200 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography using 1:3 ethylacetate/hexanes to give the N-Cbz-3,4-methanoprolinol (2.4 g)

Step 3. Synthesis of N-benzyloxycarbonyl-3,4-methanoproline (CBz-P(3,4-CH2)-OH):



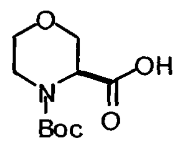
To a solution of N-Cbz-3,4-methanoprolinol (2.2 g, 8.90 mmol) in acetone (68 mL) stirring at 0 °C, was added Jones reagent (6.6 mL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to a total volume of 50 mL.] After stirring at 0 °C for 3 hours, isopropanol (11 mL) was added and stirring continued for an additional 10 minutes. The reaction mixture was diluted with water (400 mL) and extracted with ethylacetate (3 x 500 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give N-Cbz-3,4-methanoproline (2.25 g, 96%)

Example XI. Synthesis of Boc-(6S-carboethoxymethano) proline:



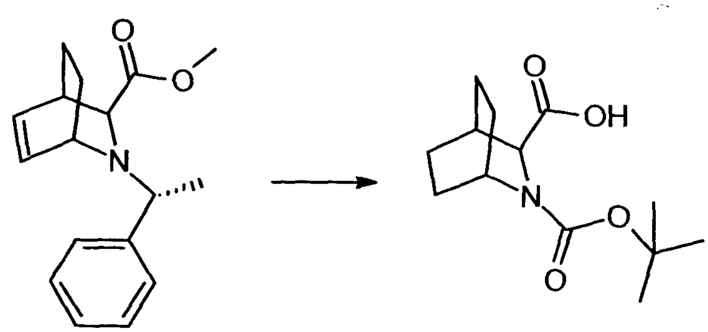
The synthesis of the title compound was carried out according to the published procedure: Marinozzi, M.; Nataini, B.; Ni, M.H.; Costantino, G.; Pellicciari R. *IL Farmaco (*1995*)* 50 (5), 327-331.

Example XII. Synthesis of Boc-3-morpholine carboxylic acid :



The synthesis of the title compound was carried out according to the published procedure: Kogami Y., Okawa, K. *Bull. Chem. Soc. Jpn.* (1987) 60, 2963-2965.

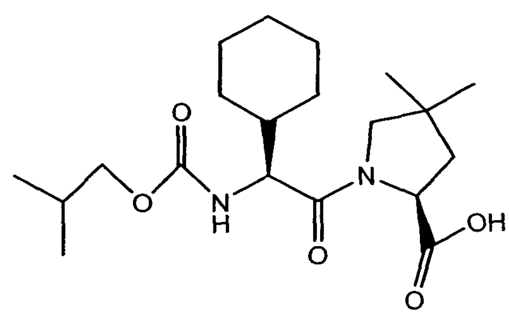
Example XIII. Synthesis of N-tert-butoxycarbonyl 2-aza-3S-hydroxycarbonyl-[2,2,2]-bicyclooctane:



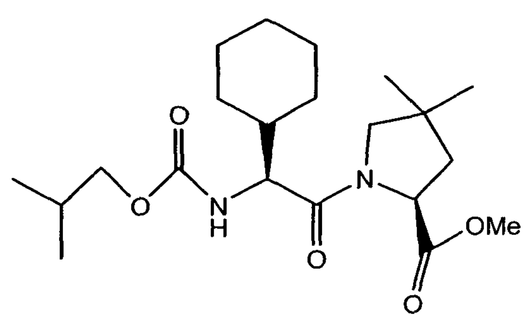
A solution of crude 2-aza-2-(1-phenylethyl)-3S-methoxycarbonyl-[2,2,2]-bicyclooct-5-ene (10 mmol) (Tetrahedron (1992) 48(44) 9707-9718) and 10% Pd on carbon (1 g) in methanol (30 mL) was acidified with 12N HCl then hydrogenated at 50 psi for 16 hours using a Parr hydrogenation apparatus. The

reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in concentrated HCl and stirred overnight. The solution was concentrated and redissolved in acetonitrile (50 mL). Diisopropylethylamine (3.5 mL) and di-tert-butyldicarbonate (1 g) were added. The reaction mixture was stirred for 24 hours and then concentrated. The residue was dissolved in CH_2Cl_2 and 5% aqueous sulfuric acid. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were concentrated. The residue was dissolved in 10% saturated sodium bicarbonate, washed with diethyl ether (2x) and acidified with 5% aqueous sulfuric acid. The aqueous layer was extracted with ethylacetate (2x). The combined ethylacetate layers were dried filtered and concentrated to give N-tert-butoxycarbonyl 2-aza-3S-hydroxycarbonyl-[2,2,2]-bicyclooctane (650 mg).

Example XIV. Synthesis of isobutyloxycarbonyl-cyclohexylglycyl-4,4-dimethyl proline (iBoc-G(Chx)-P(4,4-dimethyl)-OH):



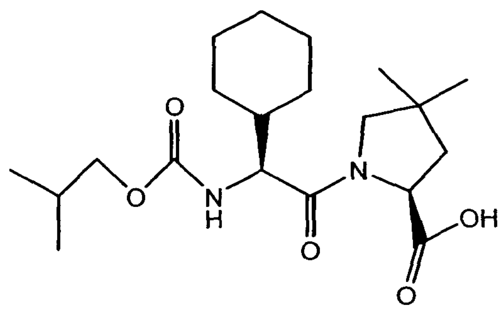
Step I. Synthesis of iBoc-G(Chx)-P(4,4-dimethyl)-OMe:



To a solution of iBoc-G(Chx)-OH (Example IX, Step 1.)(377 mg, 1.95 mmol) in acetonitrile (7 mL) was added successively HCl•HN-Pro(4,4-dimethyl)-OMe (Example I, step 6)(377 mg, 1.95 mmol), N-hydroxybenzotriazole (239 mg,

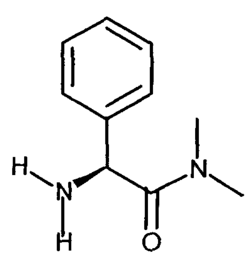
1.75 mmol), TBTU (845 mg, 2.63 mmol) and diisopropylethylamine (1.35 mL, 7.8 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate. The organic layer was washed twice with 10 ml portions of saturated sodium bicarbonate solution, 1N hydrochloric solution, and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to a white solid (612 mg, 79%).

Step 2. Synthesis of iBoc-G(Chx)-P(4,4-dimethyl)-OH:

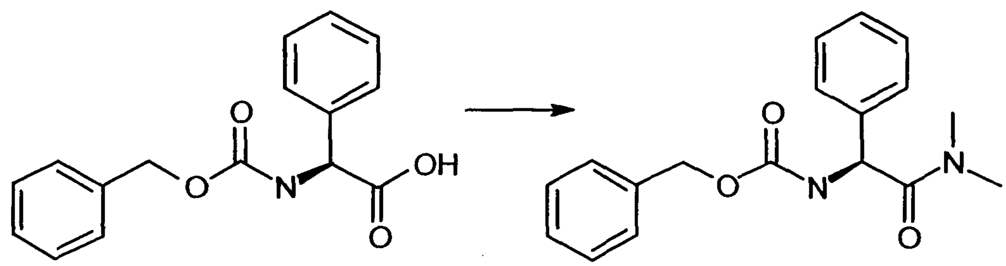


The methyl ester obtained in Step 1 above (612 mg, 1.54 mmol) in methanol (6 ml) was saponified in the presence of 2M lithium hydroxide (1.16 ml) for three hours. The methanol was removed under reduced pressure and the remaining residue was diluted with ethylacetate and acidified to pH=2 with 1N hydrochloric acid. The layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated.

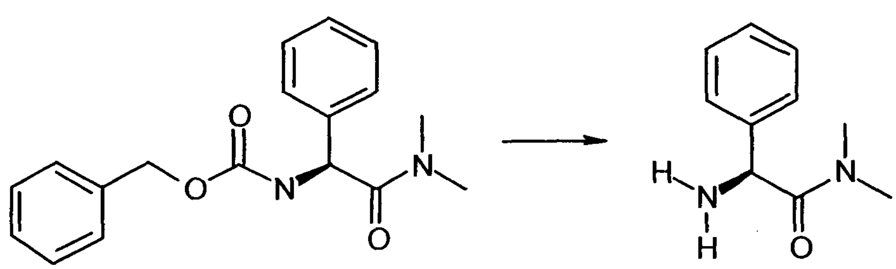
Example XV. Synthesis of L-phenylglycine dimethylamide



Step 1. Synthesis of N-benzyloxycabonyl –L-phenylglycine dimethylamide (CBz-Phg-NMe2):



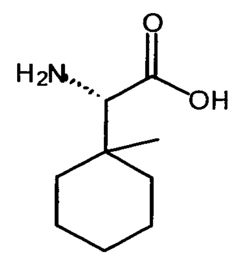
N-benzyloxycarbonyl-L-phenylglycine (25g, 88 mmols) was dissolved in THF (800mL) and cooled to -10 ^{o}C. N-methylmorpholine (9.7 mL, 88 mmols) and isobutylchloroformate (11.4 mL, 88.0 mmols) were added and the mixture allowed to stir for 1 minute. Dimethylamine (100 mL, 2M in THF) was added and the reaction was allowed to warm to room temperature. The mixture was filtered and the filtrate concentrated in *vacuo* to afford N-benzyloxycabonyl –L-phenylglycine dimethylamide (32.5 g) as a yellow oil.



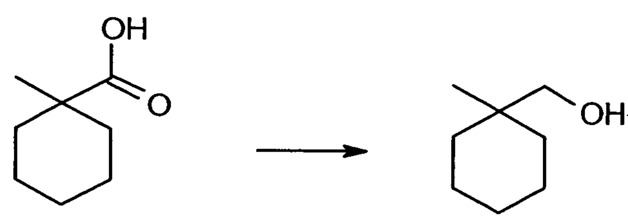
Step 2. Synthesis of L-phenylglycine dimethylamide (H-Phg-NMe2):

The N-benzyloxycarbonyl-L-phenylglycine dimethylamide (32.5 g) obtained above was dissolved in methanol (750 ml) and 10% palladium on activated carbon (3.3 g) was added. This mixture was hydrogenated on a Parr apparatus under 35 psi hydrogen for 2 hours. The reaction mixture was filtered and the solvent removed in *vacuo* and the residue recrystallized from methanol-hexanes to afford phenylglycine dimethylamide (26g) as an off white solid. The ee of this material was determined to be >99% by HPLC analysis of the 2,3,4,6-tetra-O-acetylglucopyranosylthioisocyanate derivative.

Example XVI. Synthesis of (1-methylcyclohexyl) glycine:



Step 1. 1-methyl-1-hydroxymethylcyclohexane



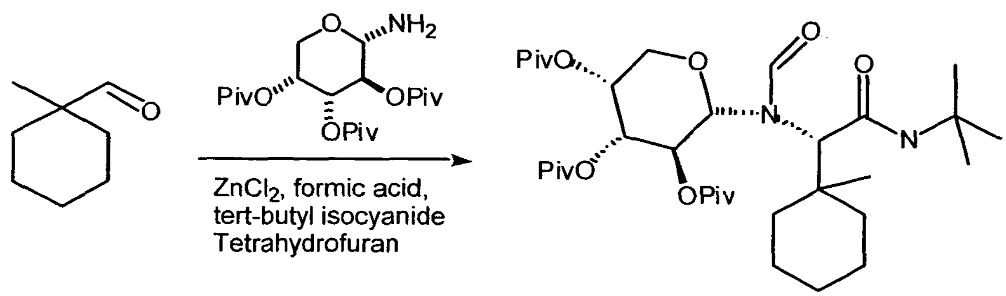
To a solution of 1-methyl-1-hydroxycarbonylcyclohexane (10 g, 70 mmol) in tetrahydrofuran(300 mL) at 0 °C was added 1M diborane in tetrahydrofuran (200 mL, 200 mmol) over 90 minutes. The cooling bath was removed and the reaction mixture was stirred at room temperature for two days. The remaining borane was quenched by the slow addition of saturated sodium bisulfate (10 mL) over 90 min with cooling. Additional saturated sodium bisulfate (200 mL) was added and after 20 min of stirring the aqueous layer was removed. The organic layer was washed with water and saturated sodium chloride, dried, filtered and concentrated. The

residue was purified by flash chromatography using 20% diethylether in hexanes to give 1-methyl-1-hydroxymethylcyclohexane (6.17 g, 48 mmol, 69%).

Step 2. 1-methylcyclohexylcarboxaldehyde:

To a solution of 1-methyl-1-hydroxymethylcyclohexane (6.17 g, 48 mmol) and triethylamine (20.1 mL, 144 mmol) in dichloromethane (150 mL) at 0 °C, was added a solution of pyridine sulfur trioxide complex (22.9 g, 144 mmol) in dimethylsulfoxide (150 mL) over 15 min. The cooling bath was allowed to warm to room temperature over two hours, at which time the reaction mixture was poured into brine with ice (400 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were diluted with hexanes (600 mL) and washed with 1M HCl (2 x 150 mL), saturated sodium chloride (2 x 100 mL), dried, filtered and concentrated. The residue was purified by flash chromatography to give 1-methylcyclohexylcarboxaldehyde (1.77 g, 13.8 mmol, 29%).

Step 3. Synthesis of N-formyl-N-glycosyl- 1-methylcyclohexyl- tert-butylamide :

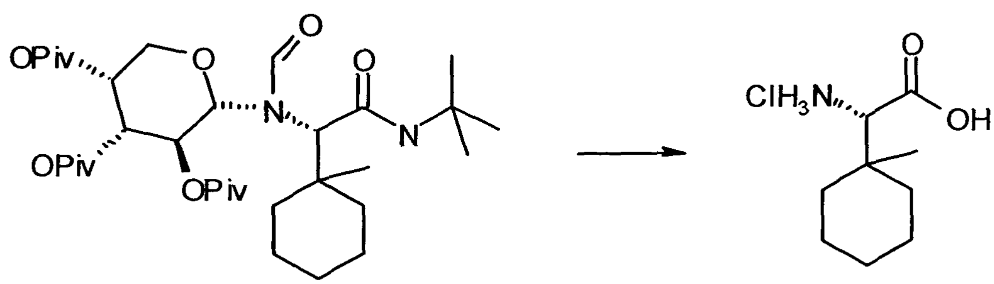


The synthesis of the 2,3,4-tri-O-pivaloyl- -D-arabinosylamine was carried out according to the published procedure (Kunz. H.; Pfrengle, W.; Ruck, K.; Wilfried, S. *Synthesis* (1991) 1039-1042).

To a solution of 1-methylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl- -D-arabinosylamine (8.3 g, 20.7 mmol), formic acid (850 µL, 22.2 mmol) and tert-butylisocyanide (2.4 mL, 21.2 mmol) in tetrahydrofuran (170

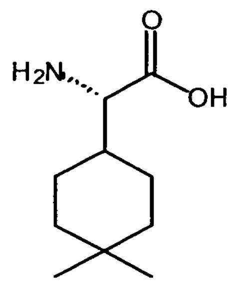
mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (41 mL, 20.57 mmol). The solution was stirred at –20 °C for 3 days, then concentrated. The residue was diluted with CH_2Cl_2 (500 mL), washed with saturated sodium bicarbonate (2 x 500 mL), water (500 mL). The organic layer was dried, filtered and concentrated to give a clear oil. Flash chromatography (20% ethylacetate in hexanes) provided pure product (4.3 g, 6.6 mmol, 33%)

Step 4. Synthesis of (1-methylcyclohexyl)glycine:

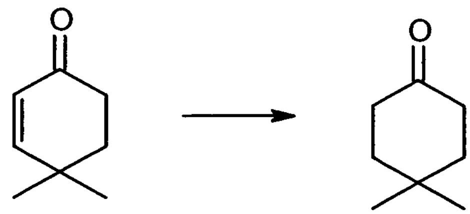


A solution of the product obtained in step 3 above (4.3 g, 6.6 mmol) in dichloromethane (30 mL) and saturated anhydrous methanolic HCl (30 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer was concentrated and the residue was dissolved in 6N HCl (50 mL) and heated at reflux for 30 hours. The solution was concentrated to give the crude (1-methylcyclohexyl)glycine hydrochloride (790 mg, 3.82 mmol, 58%).

Example XVII. Synthesis of (4,4-dimethylcyclohexyl)glycine:

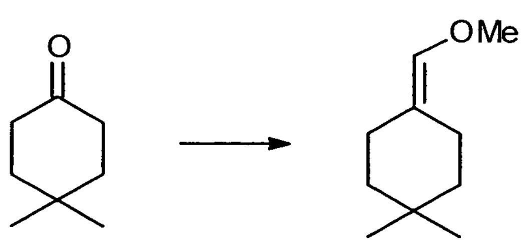


Step 1. Synthesis of 4,4-dimethylcyclohexanone:



A mixture of 4,4-dimethylcyclohex-2-en-1-one (12 mL, 91.2 mmol) and Degussa type 10% Pd on carbon (2 g) was hydrogenated at 40 psi for 18 hours. The mixture was filtered and concentrated (^{1}H NMR showed a mixture of ketone and alcohol in a 5:3 ratio). The mixture was dissolved in acetone (400 mL) and cooled to 0 °C. Jones reagent (40 mL) was added over 30 min and the cooling bath was removed. After 2 days the excess acetone was evaporated and the resulting residue was dissolved in water and diethylether. The ether layer was washed with water until colorless, dried, filtered and concentrated to give 4,4-dimethylcyclohexanone (7.4 g, 58.6 mmol, 64%).

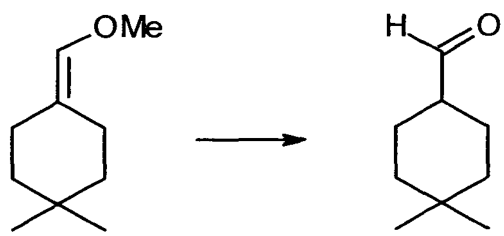
Step 2. Synthesis of the methyl enol ether of 4,4-dimethylcyclohexylcarboxaldehyde:



To a solution of methoxymethyl triphenylphosphonium chloride (8.6 g) in tetrahydrofuran (125 mL) at 0 °C was added n-butyllithium (1.6M in hexanes, 14.3

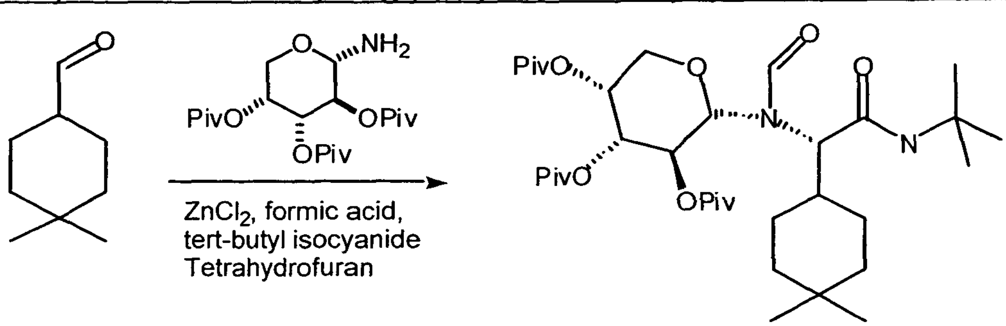
mL) over 10 min. After 30 min the reaction mixture was cooled to –78 °C and a solution of 4,4-dimethylcyclohexanone (2.45 g, 19.1 mmol) in tetrahydrofuran (50 mL) was added over 20 min. After 1 hour the cooling bath was remove and the reaction was warmed slowly to 0 °C. The reaction was diluted with saturated ammonium chloride (50 mL), ethylacetate (100 mL) and hexanes (100 mL). The organic layer was washed with water and brine, dried filtered and concentrated. The residue was stirred with hexanes (70 mL) for 10 min and filtered. The filtrate was concentrated and chromatographed using 25% ethylacetate in hexanes to give the title compound (1.925 g, 12.5 mmol, 65%).

Step 3: 4,4-dimethylcyclohexylcarboxaldehyde:



A solution of the methyl enol ether of 4,4-dimethylcyclohexylcarboxaldehyde (1.925 g, 12.5 mmol) (Step II above), tetrahydrofuran (100 mL) and 6M HCl (20 mL) was stirred at room temperature for 4 hours. The reaction mixture was diluted with hexanes, diethylether, brine and water. The organic layer was dried, filtered and concentrated to give 4,4-dimethylcyclohexylcarboxaldehyde (1.0 g, 7.1 mmol, 57%).

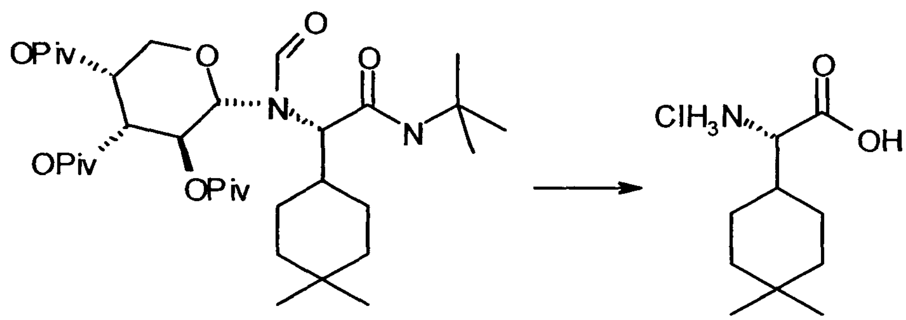
Step 4. Synthesis of N-formyl-N-glycosyl- 4,4-dimethylcyclohexyl- tert-butylamide :



To a solution of 4,4-dimethylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl-α-D-arabinosylamine (3.43 g, 8.55 mmol), formic acid

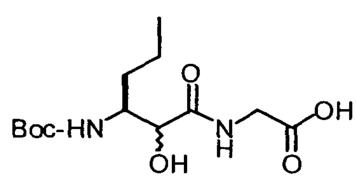
(350 µL, 9.17 mmol) and tert-butylisocyanide (990 µL, 8.76 mmol) in THF (70 mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (17 mL, 8.5 mmol). The solution was stirred at –20 °C for 2 days, then concentrated. The residue was diluted with dichloromethane (200 mL), washed with saturated sodium bicarbonate (2 x 200 mL), water (200 mL). The organic layer was dried, filtered and concentrated to give a clear oil. Flash chromatography (20% ethylacetate in hexanes) provided pure product (2.1 g, 3.3 mmol, 39%)

Step 5. Synthesis of (4,4-dimethylcyclohexyl)glycine:

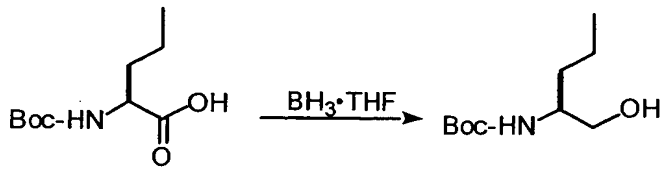


A solution of the Ugi product obtained in step 4 above (2.1 g, 3.3 mmol) in dichloromethane (20 mL) and saturated anhydrous methanolic HCl (20 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer was concentrated and the residue was dissolved in 6N HCl (40 mL) and heated at reflux for 30 hours. The solution was concentrated to give the crude (1-methylcyclohexyl)glycine hydrochloride (300 mg, 1.36 mmol, 41%).

Example XVIII. Synthesis of Boc-nVal-(CHOH)-Gly-OH:

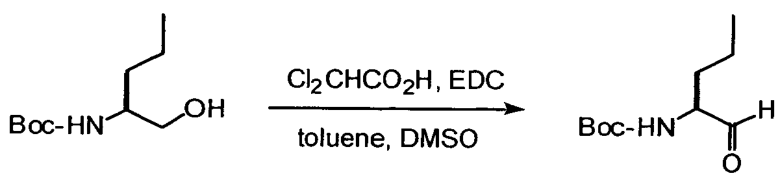


Step 1. Preparation of Boc-norvalinol:



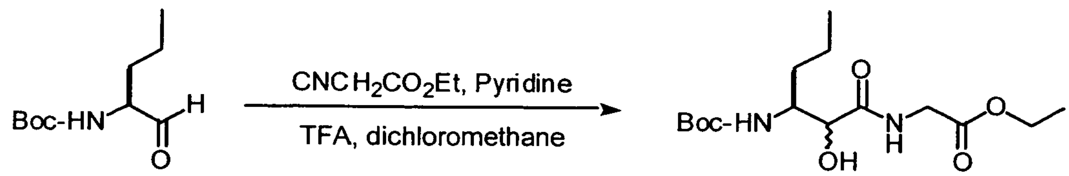
To a solution of Boc-norvaline (25.0 g, 0.115 mol) in tetrahydrofuran (461 mL), cooled to 0°C, was added borane/tetrahydrofuran complex (461 mL of a 1.0M solution in tetrahydrofuran) dropwise. After 1h at 0°C, the solution was warmed to room temperature over a period of 1.5h. TLC indicated that the reaction was complete. Methanol was added to quench the reaction. The solution was concentrated to yield the title compound (22.56 g, 96%) as a foamy syrup. TLC of the products indicated satisfactory purity. R_f = 0.34 (40% ethyl acetate/hexanes).

Step 2. Preparation Boc-norvalinal:



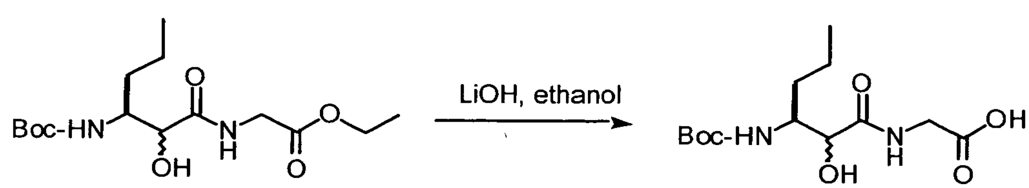
To Boc-norvalinol (7.77 g, 38 mmol), in anhydrous dimethylsulfoxide (153 mL) and toluene (153 mL) was added EDC (73.32g, 382 mmol). After the solution was cooled to 0°C, dichloroacetic acid (15.8 mL, 191 mmol) was added dropwise. After addition was complete, the reaction was stirred for 15 min. The solution was allowed to warm to room temperature over a period of 2h. The reaction mixture was concentrated to remove the toluene, then dissolved in ethyl acetate. The solution was washed successively with 1N sodium bisulfate, saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated to afford crude Boc-norvalinal which was used directly in the next step. TLC R_f = 0.84 (40% ethyl acetate/hexanes).

Step 3. Synthesis of Boc-nVal-(CHOH)-Gly-OEt:



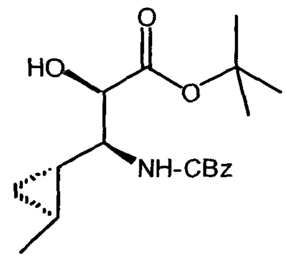
To a solution of the crude Boc-norvalinal (4.18 g, 20.77 mmol) in dichloromethane (83 mL) was added ethylisocyanoacetate (2.72 ml, 24.93 mmol) and pyridine (6.72 ml, 83.09 mmol). After the solution was cooled to 0°C, trifluoroacetic acid (4.15 ml, 41.54 mmol) was added dropwise. After stirring for 1h, the solution was stirred at room temperature for 18 hours while allowing the solvent from the reaction mixture in an uncovered vessel to evaporate under ambient conditions. The reaction mixture was concentrated, then dissolved in ethyl acetate. The solution was washed successively with 1N sodium bisulfate, saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and then concentrated. The residue was purified by flash chromatography eluting with 20% to 40% ethylacetate/hexanes to afford 2.8 g of the title compound as a yellow syrup. Low resolution mass spectroscopy confirmed the presence of the desired product (MH^+ 333).

Step 4. Synthesis of Boc-nVal-(CHOH)-Gly-OH:

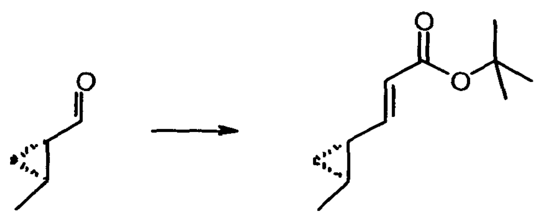


The product obtained (Boc-nVal-(CHOH)-Gly-OEt) (1.52 g, 4.70 mmol) dissolved in ethanol (23 ml) was saponified with 1N lithium hydroxide (18.81 ml) for two hours at room temperature. The reaction mixture was acidified to pH ≅ 2 with Dowex® 50 WX8 ion exchange resin, stirred for 20 minutes and then filtered. The resin was washed well with ethanol and water and the combined filtrates were concentrated to a white foam (0.48 g, 33%).

<u>Example XVIV. Synthesis of (2R,3S,4S,5S)-tert-Butyl N-CBz-3-amino-2-hydroxy-4,5 methylene-hexanoate:</u>

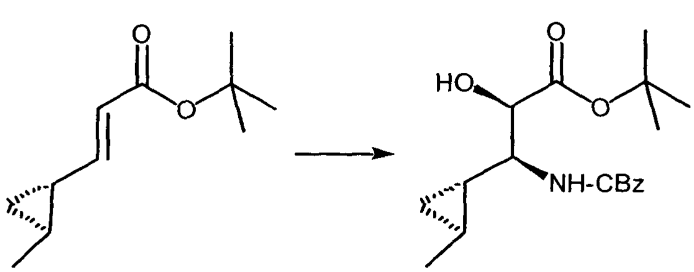


<u>Step 1:</u>



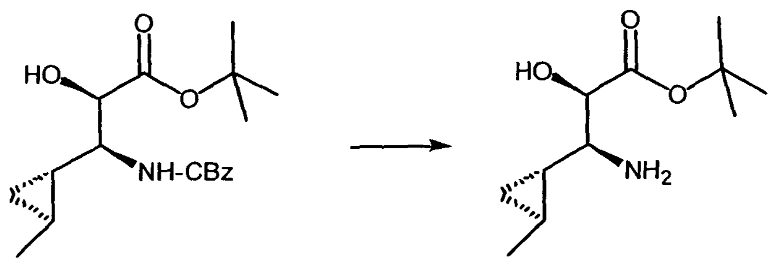
To a solution of tert-Butyl diethylphosphonoacetate (4.7 mL, 20 mmol) dissolved in THF (50 mL) at -78^{O} C was added 1.6M n-butyl lithium in hexanes (12.4 mL). After 30 minutes (1S, 2S)-2-methylcyclopropylcarboxaldehyde (1 g, 12 mmol) (Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J., *J. Org. Chem.* (1996) *61*, 3280) in diethyl ether (100 mL) was added over 10 min. The reaction was warmed to 0^{O} C for 2 hours and to 6 ^{O}C for 12 hours. The reaction was quenched with saturated ammonium chloride (20 mL) and the organic layer was separated, washed with 50 mL brine and dried over sodium sulfate, filtered and concentrated to afford 3.5 g of a clear oil. Flash chromatography (20% ethylacetate in hexanes) afforded pure unsaturated tert-butylester (1.4 g).

<u>Step 2:</u>



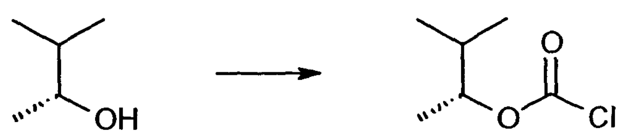
To a solution of benzyl carbamate (3.55g, 23.5 mmols) in n-propanol (24 mL) was added a solution of sodium hydroxide (900 mg ,22.7 mmol)in water (48 mL), followed by tert-butylhypochlorite (2.57 mL, 22.7 mmol). After 15 minutes the reaction was cooled to 0 ^{O}C and $(DHQ)_2$PHAL (350 mg, 0.45 mmol) was added in n-propanol (24 mL), followed by unsaturated tert-butyl ester (1.4 g) from above in n-propanol (48 mL). Finally potassium osmate (110 mg, 0.30 mmol) in water (2 mL) was added and the solution very rapidly developed a dark green color which persisted for 4 hours. After 6 hours saturated sodium sulfate (50 mL) was added and the mixture extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. Flash chromatography with 20% ethylacetate in hexanes afforded the desired cBz protected amino tert-butylester as a white solid (316 mg).

Step 3:



A mixture of CBz protected amino tert-butylester (316 mg, 0.9 mmol) and 32mg 10% palladium on carbon in 9 mL methanol was hydrogenated for 8 hours. The mixture was filtered and concentrated to afford the free amine as a clear oil (195 mg).

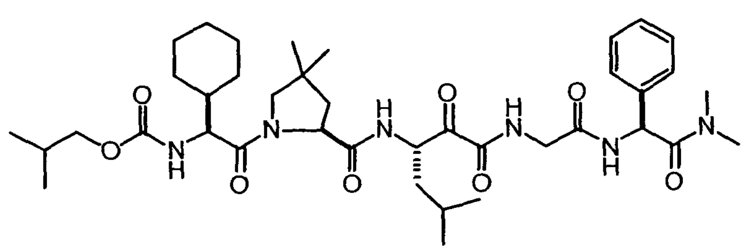
Example XX. Synthesis of 1R,2-dimethylPropyl chloroformate:



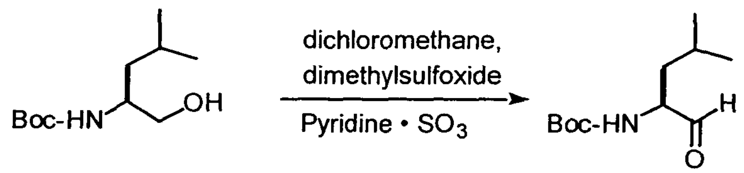
To the commercially available 2R-hydroxy-3-methylbutane (410 mg, 4.65 mmol) was added a solution of 20% phosgene in toluene (1 mL, 2 mmol). The solution was stirred for 6 hours to generate the chloroformate (2 mmol) which was reacted directly and immediately with the desired amine. The S-isomer was synthesized by the same procedure.

II) Representative solution phase synthesis of HCV inhibitors

Example XXI. Solution phase synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CO)-Gly-Phg-dimethylamide:

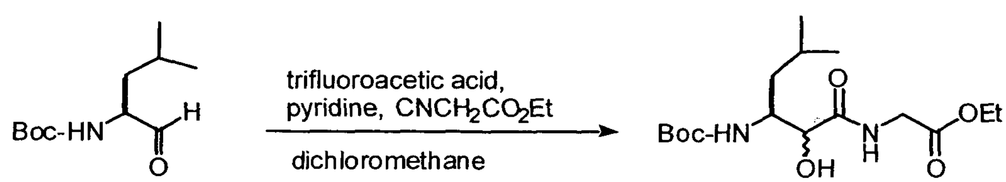


Step 1. Synthesis of tert-butyloxycarbonyl-leucinal (Boc-Leu-CHO):



To a solution of the commercially available (Advanced Chem Tech) Boc-L-leucinol (0.78 g, 3.6 mmol) in anhydrous dichloromethane (17.5 ml) was added triethyl amine (2 ml, 14.36 mmol) and the mixture was cooled to 0 °C. Dimethyl sulfoxide (17.5 ml) was added followed by sulfur trioxide pyridine complex (2.3 g, 14.36 mmol) and the reaction was stirred for two hours. TLC in 1:1 ethylacetate: hexanes confirmed the completion of the reaction. The reaction mixture was concentrated and the remaining residue diluted with ethylacetate. The ethylacetate layer was washed with 1M hydrochloric acid (2 × 75 ml) followed by saturated sodium bicarbonate solution (2 × 75 ml) and brine (75 ml). The organic layer was dried (sodium sulfate), filtered and concentrated to yield 775 mg of product.

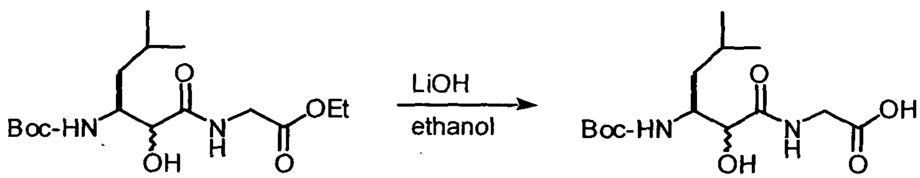
<u>Step 2. Synthesis of Boc-2-hydroxy-3-amino-5-methyl hexanoyl-glycine ethyl ester (Boc-Leu-(CHOH)-Gly-OEt):</u>



To a solution of Boc-Leucine aldehyde (0.77 g, 3.59 mmol) in anhydrous dichloromethane (24 ml) was added anhydrous pyridine (1.16 ml, 14.36 mmol) and ethylisocyanoacetate (0.4 ml, 4.66 mmol). The reaction mixture was cooled to 0 °C and trifluoroacetic acid (0.55 ml, 7/18 mmol) was added over two minutes. The reaction mixture was capped and stirred at 4 °C for four days, and at room temperature for one day. The reaction mixture was diluted with dichloromethane (350 ml) and washed twice each with 75 ml portions of 1M hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was dried, filtered and concentrated. The residue obtained was subjected to flash chromatography in a

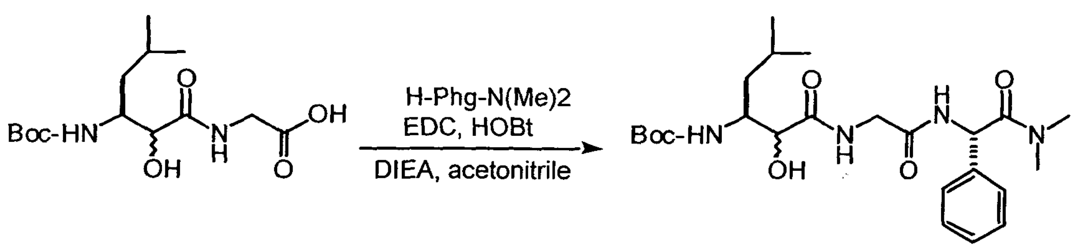
2" × 6" silica gel column using 10% ethylacetate in hexanes (800 ml) followed by 1:1 ethylacetate in hexanes (800 ml). The fractions corresponding to the product were pooled and concentrated to yield 980 mg (79%) product.

Step 3. Synthesis of Boc-Leu-(CHOH)-Gly-OH:



To a solution of Boc-Leu-(CHOH)-Gly-Oet (0.98 g, 2.83 mmol) in ethanol (11.3 ml) was added 2M lithium hydroxide (4.25 ml) and the reaction was stirred for five hours at room temperature. The ethanol was removed under reduced pressure and the aqueous layer was diluted with ethylacetate. The organic layer was washed with 1M hydrochloric acid followed by brine, dried, filtered and concentrated to yield 775 mg (86%) product as a white solid.

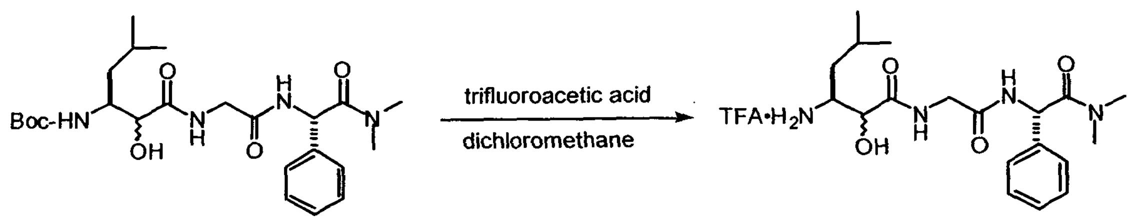
Step 4. Synthesis of Boc-Leu-(CHOH)-Gly-Phg-dimethylamide:



To a solution of Boc-Leu-(CHOH)-Gly-OH (0.37 g, 1.18 mmol) in acetonitrile (23 ml) was added successively phenylglycine dimethylamide (obtained in Example XV, Step 2), EDC (0.34 g, 1.76 mmol), N-hydroxybenzotriazole (HOBt)(0.18 g, 1.18 mmol) and diisopropylethylamine (DIEA) (0.82 ml, 4.7 mmol) and the reaction was stirred for 18 hours at room temperature. The reaction mixture was concentrated and the remaining residue was diluted with ethylacetate and washed successively with two 75 ml portions of 1M hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was then dried filtered and concentrated. The crude product was subjected to

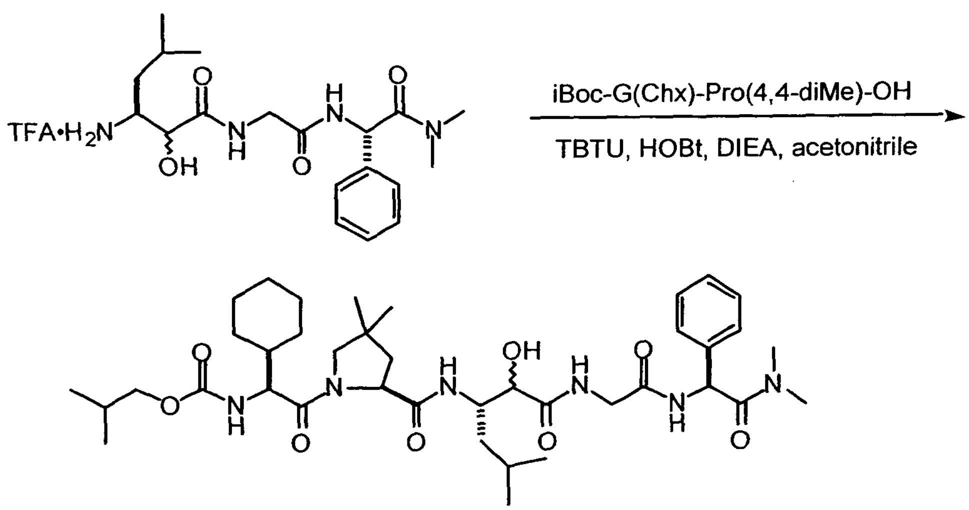
flash chromatography in a 2" × 6" silica gel column using 4:1 ethylacetate: hexanes (700 ml) followed by ethylacetate (1000 ml) and 10% methanol in dichloromethane (600 ml). The fractions corresponding to the product were pooled and concentrated to yield 445 mg (80%) white solid.

Step 5. Synthesis of H-Leu-(CHOH)-Gly-Phg-dimethylamide trifluoroacetate salt:



To a solution Boc-Leu-(CHOH)-Gly-Phg-dimethylamide (70 mg, 0.146 mmol) in dichloromethane (1 ml) was added trifluoroacetic acid (1 ml) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was concentrated and taken to the next step without further purification.

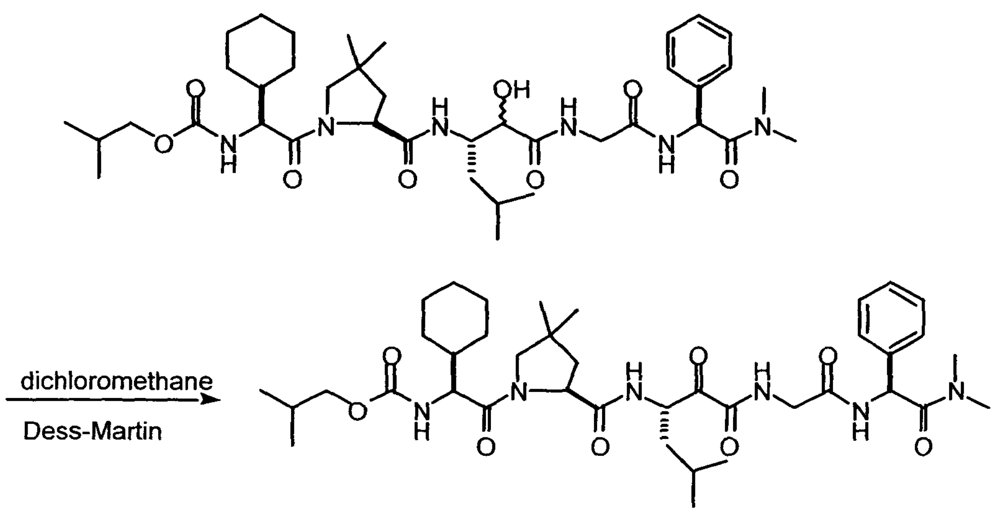
Step 6. Synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CHOH)-Gly-Phg-dimethylamide:



To a solution of iBoc-G(Chx)-P(4,4-diMe)-OH (Example XIV, step 2)(53 mg, 0.148 mmol) in acetonitrile (3 ml) was added successively TFA•2HN-Leu(CHOH)-Gly-Phg-NMe2 (61 mg, 0.148 mmol), N-Hydroxybenzotriazole (HOBt) (23 mg, 0.148 mmol), TBTU (71.5 mg, 0.222 mmol and diisopropylethyl amine (103 l,

0.593 mmol). The reaction was stirred at room temperature for 18 hours and concentrated. The remaining residue was dissolved in ethylacetate and washed with 1M hydrochloric acid (2 × 5 ml), saturated sodium bicarbonate solution (2 × 5 ml), and brine (2 × 5 ml). The organic layer was dried, filtered and concentrated. The product (100 mg) was taken to the next step without further purification.

Step 7. Synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CO)-Gly-Phg-dimethylamide:



To a solution of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CHOH)-Gly-Phg-dimethylamide (30 mg, 0.04 mmol) in dichloromethane (1 ml) was added the commercially available Dess-Martin reagent (Omega Chemical Company Inc.)(67.8 mg, 0.16 mmol) and the reaction was stirred at room temperature for 90 minutes. The reaction mixture was concentrated and the remaining residue was stirred in 5% sodium thiosulfate. It was then diluted with dichloromethane and the layers were separated. The organic layer was washed with sodium thiosulfate (4 × 3 ml), followed by water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was dissolved in hexanes and isopropyl alcohol and was subjected to HPLC purification using a normal phase Kromasil 5 silica column (Phenomenex, 250 × 21.20 mm, 100 angstrom pore size, 5 μm gel particles) eluting with a 30 minutes gradient consisting of 0 to

25% isopropyl alcohol in hexanes (25 ml/minutes). The fractions corresponding to the product were pooled and concentrated. Lyophilization from water yielded 6.7 mg white powder. Low resolution mass spectra confirmed the desired mass (MH^+ = 741.4).

<u>III) Solid Phase Synthesis:</u>

Solid-phase synthesis is useful for the production of small amounts of certain compounds of the present invention. As with the conventional solid-phase synthesis of peptides, reactors for the solid-phase synthesis of peptidyl ketoamides are comprised of a reactor vessel with at least one surface permeable to solvent and dissolved reagents, but not permeable to synthesis resin of the selected mesh size. Such reactors include glass solid phase reaction vessels with a sintered glass frit, polypropylene tubes or columns with frits, or reactor Kans™ made by Irori Inc., San Diego CA. The type of reactor chosen depends on volume of solid-phase resin needed, and different reactor types might be used at different stages of a synthesis. The following procedures will be referenced in the subsequent examples:

<u>Procedure A:</u> *Coupling reaction*: To the resin suspended in N-methylpyrrolidine (NMP) (10-15 mL/ gram resin) was added Fmoc-amino acid (2 eq), HOAt (2 eq), HATU (2 eq) and diisopropylethylamine (4 eq). The mixture was let to react for 4-48 hours. The reactants were drained and the resin was washed successively with dimethylformamide, dichloromethane, methanol, dichloromethane and diethylether (use 10-15 mL solvent/ gram resin). The resin was then dried in vacuo.

<u>Procedure B:</u> *Fmoc deprotection*: The Fmoc-protected resin was treated with 20% piperidine in dimethylformamide (10 mL reagent/ g resin) for 30 minutes. The reagents were drained and the resin was washed successively with

dimethylformamide, dichloromethane, methanol, dichloromethane and diethyl ether (10 mL solvent/ gram resin).

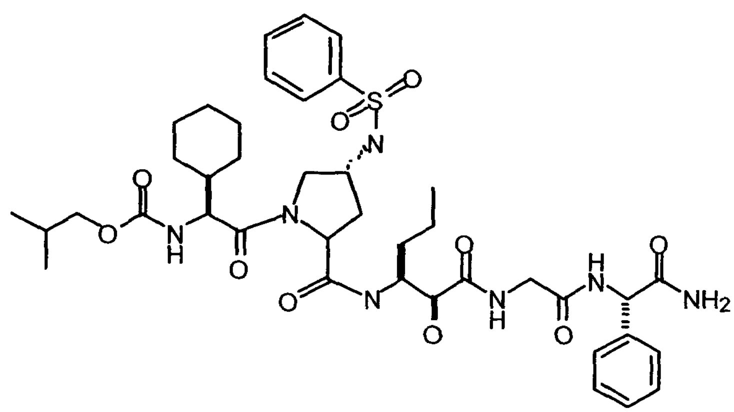
Procedure C: *Boc deprotection*: The Boc-protected resin was treated with a 1:1 mixture of dichloromethane and trifluoroacetic acid for 20-60 minutes (10 mL solvent/ gram resin). The reagents were drained and the resin was washed successively with dichloromethane, dimethylformamide, 5% diisopropylethylamine in dimethylformamide, dimethylformamide, dichloromethane and dimethylformamide (10 mL solvent/ gram resin).

Procedure D: *Semicarbazone hydrolysis*: The resin was suspended in the cleavage cocktail (10 mL/ g resin) consisting of trifluoroacetic acid: pyruvic acid: dichloromethane: water 9:2:2:1 for 2 hours. The reactants were drained and the procedure was repeated three more times. The resin was washed successively with dichloromethane, water and dichloromethane and dried under vacuum.

Procedure E: *HF cleavage*: The dried peptide-nVal(CO)-G-O-PAM resin (50 mg) was placed in an HF vessel containing a small stir bar. Anisole (10% of total volume) was added as a scavenger. In the presence of glutamic acid and cysteine amino acids, thioanisole (10%) and 1,2-ethanedithiol (0.2%) were also added. The HF vessel was then hooked up to the HF apparatus (Immuno Dynamics) and the system was flushed with nitrogen for five minutes. It was then cooled down to -70°C with a dry ice/ isopropanol bath. After 20 minutes, HF was distilled to the desired volume (10 mL HF/ g resin). The reaction was let to proceed for one and a half hour at 0°C. Work up consisted of removing all the HF using nitrogen. Dichloromethane was then added to the resin and the mixture was stirred for five minutes. This was followed by the addition of 20% acetic acid in water (4 mL). After stirring for 20 minutes, the resin was filtered using a fritted funnel and the dichloromethane was removed under reduced pressure. The remaining residue and the mixture was washed with hexanes (2×) to remove scavengers. Meanwhile, the resin was soaked in 1 mL methanol. The aqueous

layer (20% HOAc) was added back to the resin and the mixture was agitated for five minutes and then filtered. The methanol was removed under reduced pressure and the aqueous layer was lyophilized. The peptide was then dissolved in 10-25% methanol (containing 0.1% trifluoroacetic acid) and purified by reverse phase HPLC.

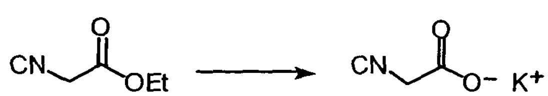
Example XXII: Representative solid phase Synthesis of Hep C inhibitors: (iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-NH2)



Step 1. Synthesis of Fmoc-nV-(dpsc)-Gly-OH:

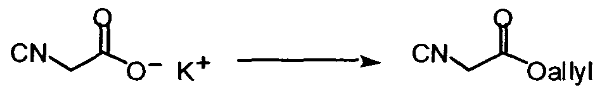
A) Synthesis of allyl isocyanoacetate (steps a-b below):

a) Synthesis of isocyanoacetic acid potassium salt:



Ethyl isocyanoacetate (96.6 ml, 0.88 mol) was added dropwise to a chilled solution of ethanol (1.5 L) and potassium hydroxide (59.52 g, 1.0 mol). The reaction was slowly warmed to room temperature. After two hours the precipitated product was filtered on a glass funnel and washed with several portions of chilled ethanol. The potassium salt of isocyanoacetic acid thus obtained was dried in vacuo to a golden-brown solid (99.92 g, 91.8%).

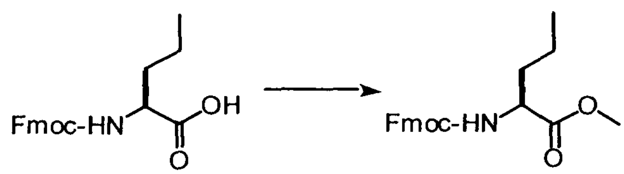
b) Synthesis of allyl isocyanoacetate:



To the product of part a (99.92 g, 0.81 mol) dissolved in acetonitrile (810 ml) was added allyl bromide (92 ml, 1.05 mol). After heating at reflux for four hours a dark brown solution was obtained. The reaction mixture was concentrated and the remaining residue was dissolved in ether (1.5 L) and washed three times with water (500 ml). The organic layer was dried, filtered and concentrated to a dark brown syrup. The crude was purified by vacuum distillation at 7 mm Hg (98 C) to a clear oil (78.92 g, 78%). NMR δ ppm ($CDCl_3$): 5.9 (m, 1 H), 5.3 (m, 2H), 4.7 (d, 2H), 4.25 (s, 2H).

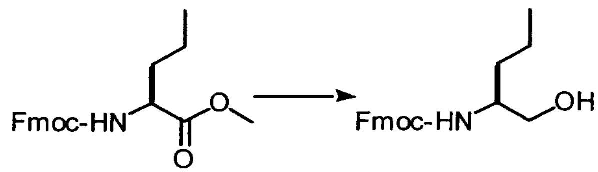
<u>B) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinal (steps a-c below):</u>

a) Synthesis of 9-fluorenylmethoxycarbonyl-L-norvaline methyl ester (Fmoc-nVal-OMe):



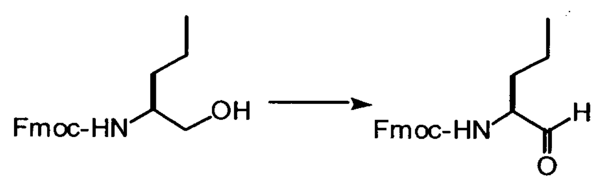
To a chilled solution of the commercially available Fmoc-norvaline (25 g, 73.75 mmol) in anhydrous methanol (469 ml) was added thionyl chloride (53.76 ml, 737.5 mmol) over one hour. TLC in ethylacetate taken an hour later confirmed the completion of the reaction (R_f = 0.85). The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate. The organic layer was washed with several 200 ml portions of saturated sodium bicarbonate followed by brine. The organic layer was dried, filtered and concentrated to afford Fmoc-norVal-OMe) as a white solid (26.03 g) in quantitative yield. NMR δ ppm (CD_3OD): 7.7 (m, 2H), 7.6 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 4.3 (m, 2H), 4.1 (m, 2H), 3.7 (s, 3H), 1.7 (m, 1H), 1.6 (m, 1H), 1.4 (m, 2H), 0.95 (t, 3H).

b) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinol (Fmoc-nValinol):



To Fmoc-nVal-OMe (26.03 g, 73.75 mmol) in tetrahydrofuran (123 ml) and methanol (246 ml) was added calcium chloride (16.37 g, 147.49 mmol). The reaction mixture was cooled to 0°C and sodium borohydride (11.16 g, 294.98 mmol) was added in several batches. To the thick paste obtained, methanol (500 ml) was added and the reaction was let to stir at room temperature for 90 minutes. TLC in 2:3 ethylacetate: hexanes confirmed the completion of the reaction (R_f = 0.25). The reaction was quenched with the slow addition of water (100 ml) at 0°C. The methanol was removed under reduced pressure and the remaining aqueous phase was diluted with ethylacetate. The organic layer was washed with water (3 × 500 ml), saturated sodium bicarbonate (3 × 500 ml) and brine (500 ml). The organic layer was dried over sodium sulfate, filtered and concentrated to a white solid (21.70 g, 90.5%). NMR δ ppm (CD_3OD): 7.8 (m, 2H), 7.7 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 4.3-4.5 (m, 2H), 4.2 (m, 1H), 3.6 (s, 1H), 3.5 (s, 2H), 1.5 (m, 1H), 1.3-1.4 (m, 3H), 0.99 (m, 3H).

c) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinal (Fmoc-nVal-CHO):

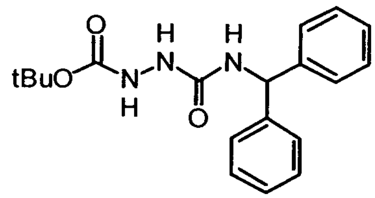


To a solution of Fmoc-norValinol (21.70 g, 66.77 mmol) in dichloromethane (668 ml) was added triethylamine (37.23 ml, 267 mmol) and the solution was cooled to 0°C. A suspension of pyridine sulfur trioxide complex (42.51 g, 267 mmol) in dimethylsulfoxide (96 ml) was added to the chilled solution. After one hour, TLC in 2:3 ethylacetate: hexanes confirmed the completion of the reaction. The dichloromethane was removed under reduced pressure and the remaining residue was dissolved in ethylacetate and washed with water (2 × 50 ml), 1N

saturated sodium bisulfate (2 × 50 ml), saturated sodium bicarbonate (2 × 50 ml) and brine (50 ml). The organic layer was concentrated to yield a white solid. Theoretical yield (21.57 g) was assumed and the reaction was taken to the next step without further purification.

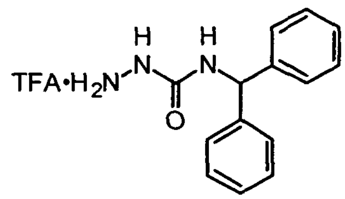
<u>C) Synthesis of diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt (steps a-b below):</u>

a) Synthesis of Boc-semicarbazid-4-yl diphenylmethane



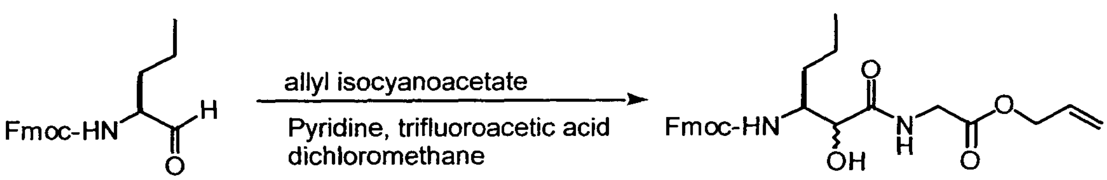
To a solution of carbonyldiimidazole (16.2 g, 0.10 mole) in dimethylformamide (225 ml) was added a solution of t-butyl carbazate (13.2 g, 0.100 mol) in dimethylformamide (225 ml) dropwise over 30 minutes. Diphenylmethylamine (18.3 g, 0.10 mol) was added next over 30 minutes. The reaction was allowed to stir at room temperature for one hour. Water (10 mL) was added and the mixture was concentrated to about 150 mL under reduced pressure. This solution was poured into water (500 mL) and extracted with ethyl acetate (400 mL). The ethylacetate phase was washed two times each with 75 mL 1N HCl, water, saturated sodium bicarbonate solution and sodium chloride, and dried with magnesium sulfate. The mixture was filtered and the solution was concentrated to give 29.5 g (85% yield) of a white foam. This material could be purified by recrystallization from ethyl acetate/hexane, but was pure enough to use directly in the next step: mp 142-143°C. ^{1}H NMR ($CDCl_3$) d 1.45 (s, 9H), 6.10 (dd, 2H), 6.42 (s, 1H), 6.67 (bs, 1H), 7.21-7.31 (m, 10H). Anal calculated for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.46; H, 6.75; N; 12.90.

b) Synthesis of diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt



A solution of Boc-semicarbazid-4-yl diphenylmethane (3.43 g, 10 mmol) in dichloromethane (12.5 mL) was treated with 12.5 mL of trifluoroacetic acid at room temperature and stirred for 30 min. The solution was added dropwise to 75 mL of ether and the resulting solid (2.7 g, 80%) was collected by filtration. mp 182-184°C. ^1H NMR (CD_3OD) d 6.05 (s, 1H), 7.21-7.35 (m, 10H). ^{13}C NMR (CD_3OD) d 57.6, 118.3 (q, CF_3), 126.7, 127.9, 141.6, 156.9, 160.9 (q, $CF_3\underline{C}O_2H$).

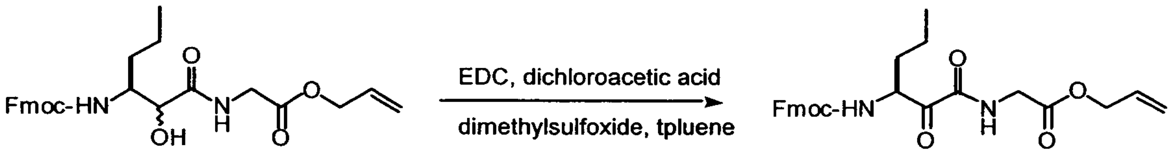
D) Synthesis of Fmoc-nVal-(CHOH)-Gly-Oallyl:



To a solution of Fmoc-nVal-CHO (Step IB) (5.47 g, 16.90 mmol) in dichloromethane (170 ml) was added allyl isocyanoacetate (Step IA) (2.46 ml, 20.28 mmol) and pyridine (5.47 ml, 67.61 mmol). The reaction mixture was cooled to 0°C and trifluoroacetic acid (3.38 ml, 33.80 mmol) was added dropwise. The reaction was stirred at 0°C for 1h, and then at room temperature for 48 hours. TLC taken in ethylacetate confirmed the completion of the reaction. The reaction mixture was concentrated and subjected to flash chromatography using 20% to 70% ethylacetate in hexanes. Fractions containing the desired product were pooled and concentrated to a white foam (6.88 g, 87.3%). TLC in 50:50 ethylacetate shows one spot (R_f = 0.37). NMR δ ppm (CD_3OD): 7.8 (m, 2H), 7.65 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 5.9 (m, 1H), 5.1-5.4 (m, 2H), 4.55-4.65 (m, 2H),

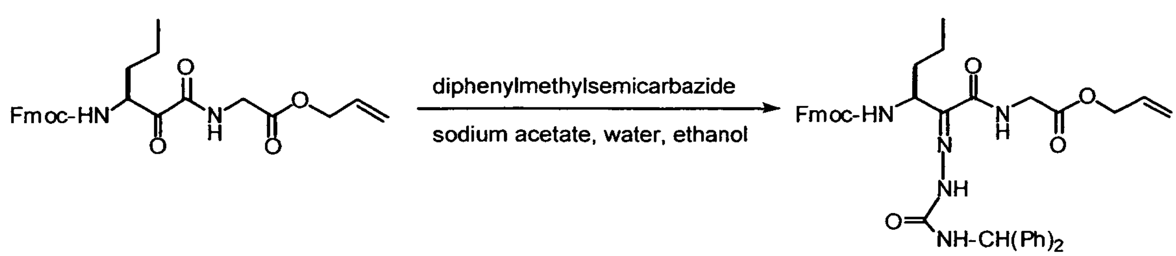
4.3-4.4 (m, 2H), 4.15-4.25 (m, 1H), 4.01 (s, 1H), 3.9-4.0 (m, 3H), 1.5-1.6 (m, 2H), 1.35-1.45 (m, 3H), 0.9 (m, 3H).

E) Synthesis of Fmoc-nVal-(CO)-Gly-Oallyl:



to a solution of Fmoc-nVal-(CHOH)-Gly-Oallyl (Step D) (5.01 g, 10.77 mmol) in dimethylsulfoxide (100 ml) and toluene (100 ml) was added EDC (20.6 g, 107.7 mmol). The reaction mixture was cooled to 0 °C and dichloroacetic acid (4.44 ml, 53.83 mmol) was added dropwise. The reaction was stirred for 15 minutes at 0 °C and 1h at room temperature. After cooling back to 0 C, water (70 ml) was added and the toluene was removed under reduced pressure. The remaining residue was diluted with ethylacetate and washed several times with a saturated sodium bicarbonate solution followed by 1N sodium bisulfate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The theoretical yield of 4.99 g was assumed and the reaction was taken to the next step without further purification. TLC in 50:50 ethylacetate shows one spot (Rf = 0.73).

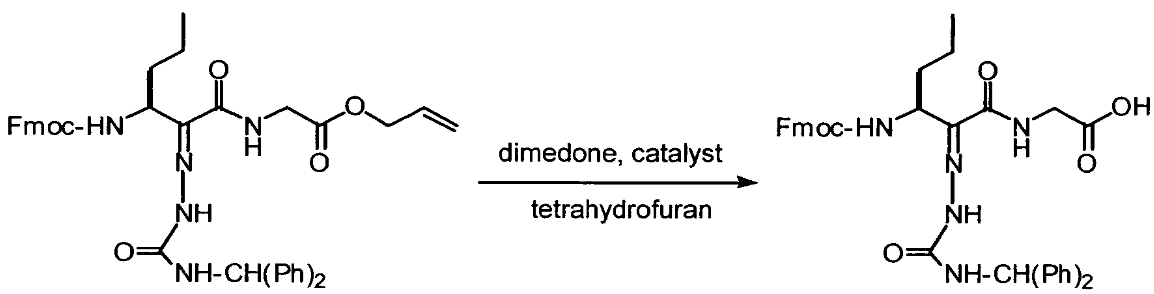
F) Synthesis of Fmoc-nVal-(dpsc)-Gly-Oallyl:



To a solution of Fmoc-nVal-(CO)-Gly-Oallyl (Step E) (4.99 g, 10.75 mmol) in ethanol (130 ml) and water (42 ml) was added diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt (Step IC) (7.6 g, 21.5 mmol) and sodium acetate •$3H_2O$ (1.76 g, 12.9 mmol), successively . The reaction mixture was heated at

reflux for 90 minutes. The completion of reaction was confirmed by TLC taken in 1:1 ethylacetate: hexane. Ethanol was removed under reduced pressure and the remaining residue was dissolved in ethylacetate and washed with 1N sodium bisulfate (2 × 10 ml), saturated sodium bicarbonate (2 × 10 ml), followed by brine (10 ml). The organic layer was dried, filtered and concentrated. The resulting residue was purified by flash chromatography in 20% to 50% ethylacetate in hexanes to give a white solid (5.76g, 78%). TLC in 50:50 ethylacetate: hexanes showed two spots (cis and trans isomers) with R_f = 0.42 and 0.5.

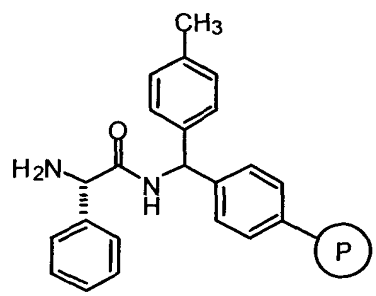
G) Synthesis of Fmoc-nVal-(dpsc)-Gly-OH:



To a solution of Fmoc-nVal-(dpsc)-Gly-Oallyl (Step IG) (4.53 g, 6.59 mmol) in tetrahydrofuran (300 ml) was added dimedone (4.62 g, 32.97 mmol) followed by tetrakis(triphenylphosphine) palladium(0) catalyst (0.76 g, 0.66 mmol). The completion of the reaction was confirmed by TLC after 90 minutes using 9:1 dichloromethane: methanol. The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate and washed three times with 50 ml portions of 0.1M potassium biphosphate. The organic layer was then treated with 50 ml sodium bisulfite and the two phase system was stirred for 15 minutes. The phases were separated and the procedure was repeated twice more. The organic layer was dried and concentrated and subjected to flash chromatography with 20% to 100% ethylacetate in hexanes. This was followed with 9:1 dichloromethane: methanol solution. The fractions corresponding to the pure product were pooled and concentrated to obtain a white solid (3.99 g, 94%). TLC

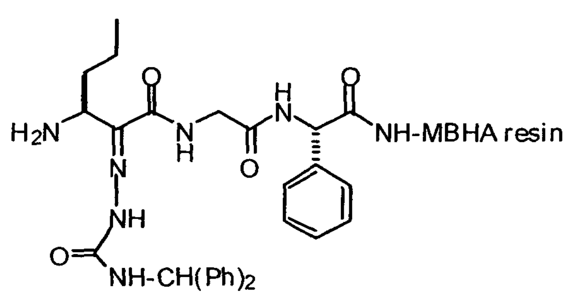
in 9:1 dichloromethane: methanol showed two spots (cis and trans isomers). NMR δ ppm (CD_3OD): 7.75 (m, 2H), 7.6 (m, 3H), 7.2-7.4 (m, 14H), 6.1-6.2 (m, 1H), 4.25-4.4 (m, 2H), 4.1-4.2 (m, 2H), 3.85 (s, 2H), 1.6-1.8 (m, 2H), 1.3-1.5 (m, 2H), 0.95 (t, 3H).

Step 2. Synthesis H-Phg-MBHA resin:



The commercially available MBHA resin (2.6 g, 1.12 mmol/g, 2.91 mmol) was transferred to a 250 mL fritted solid phase reaction vessel equipped with a nitrogen inlet. It was then washed thoroughly with 30 ml portions of dichloromethane, methanol, dimethylformamide and dichloromethane and coupled over 18 hours to the commercially available Fmoc-Phg-OH (2.17 g, 5.82 mmol) according Procedure A with 99.82% efficiency. The resin was then subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

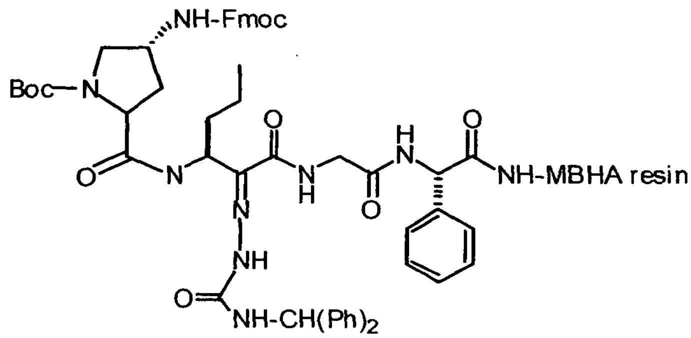
Step 3. Synthesis of H-nVal(dpsc)-Gly-Phg-MBHA resin:



The resin obtained in step II (2.6 g, 0.8 mmol/g, 2.91 mmol) was reacted with Fmoc-nVal-(dpsc)-Gly-Oallyl (Step IG) (5.82 mmol, 3.77 g) according to

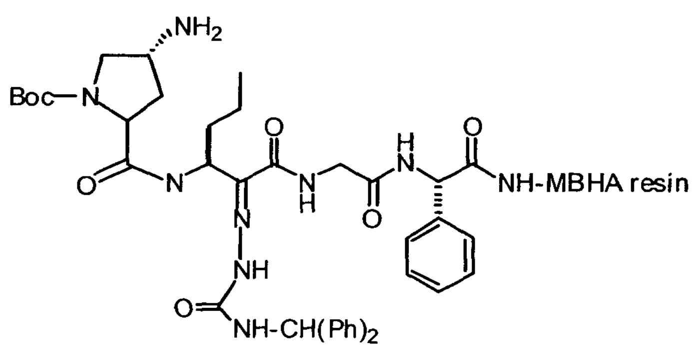
Procedure A. After 18 hours, quantitative ninhydrin analysis indicated 99.91% coupling efficiency. The resin was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

Step 4. Synthesis of Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA resin:



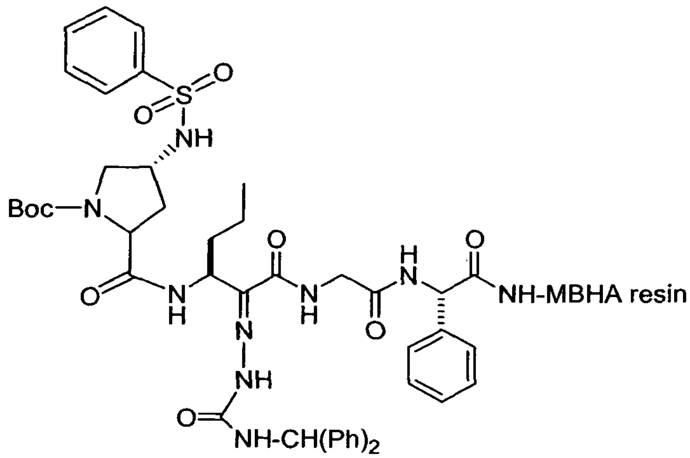
The compound H-nVal(dpsc)-Gly-Phg-MBHA resin (Step 3 above) (600 mg, 0.8 mmol/g, 0.67 mmol) was transferred to a fritted polypropylene tube and was coupled to Boc-Pro(4t-NHFmoc)-OH (Example VI, Step 3) (610 mg, 1.34 mmol) according to procedure A. After 18 hours, quantitative ninhydrin analysis indicated 99.96% coupling efficiency.

Step 5. Synthesis of Boc-Pro(4t-NH_2)-nVal(dpsc)-Gly-Phg-MBHA resin:



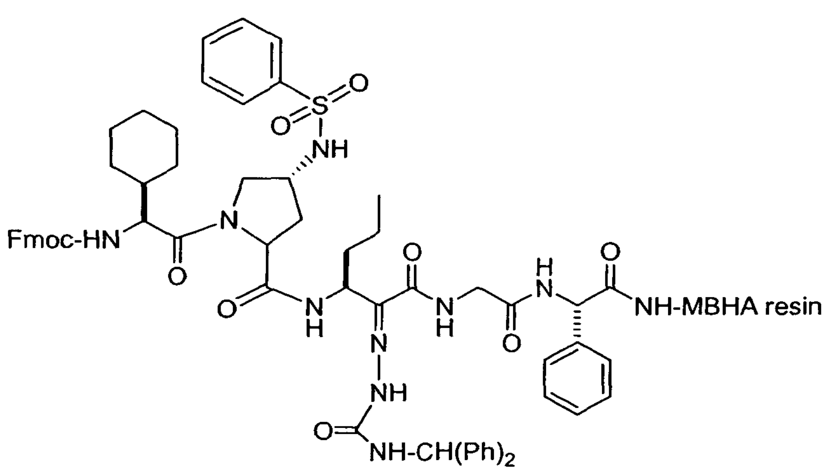
The resin from the previous step (Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

Step 6. Synthesis of Boc-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA resin:



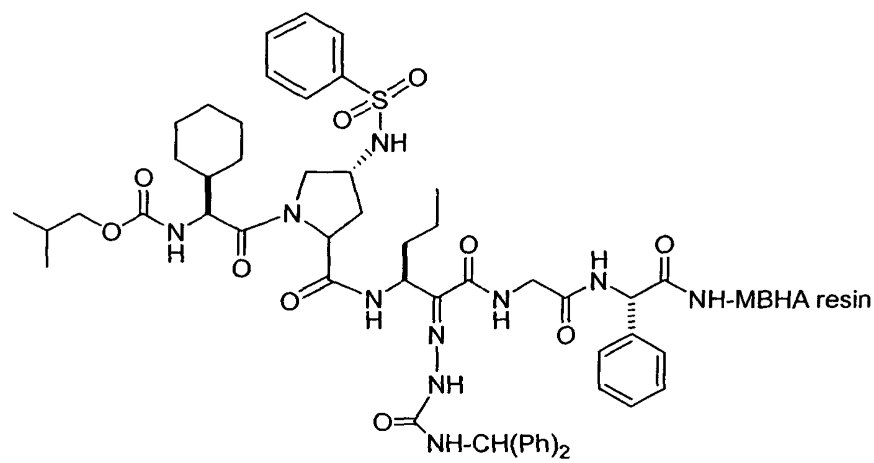
To the resin obtained from the previous step (Boc-Pro(4t-NH_2)-nVal(dpsc)-Gly-Phg-MBHA resin) (0.2 g, 0.22 mmol) suspended in NMP (2 ml) was added 2,4,6-collidine (0.24 ml, 1.79 mmol) and benzenesulfonyl chloride and the reaction was shaken for 18 hours. The solvent was drained and the resin was washed thoroughly with 2 ml portions of dichloromethane, methanol, dimethylformamide and dichloromethane. Qualitative ninhydrin analysis showed colorless beads and solution indicating a successful reaction.

Step 7. Synthesis of Fmoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA resin:



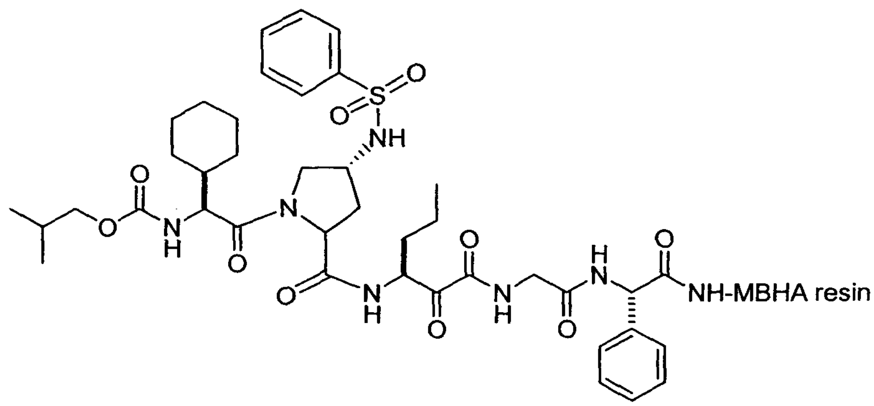
The resin obtained in the previous step (Boc-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to the Boc deprotection procedure according to Procedure C. Fmoc-G(Chx) (0.17 g, 0.45 mmol) was then coupled according to procedure A. After 18 hours qualitative ninhydrin analysis showed colorless beads and the quantitative ninhydrin analysis indicated 99.79% coupling efficiency.

Step 8. Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin:



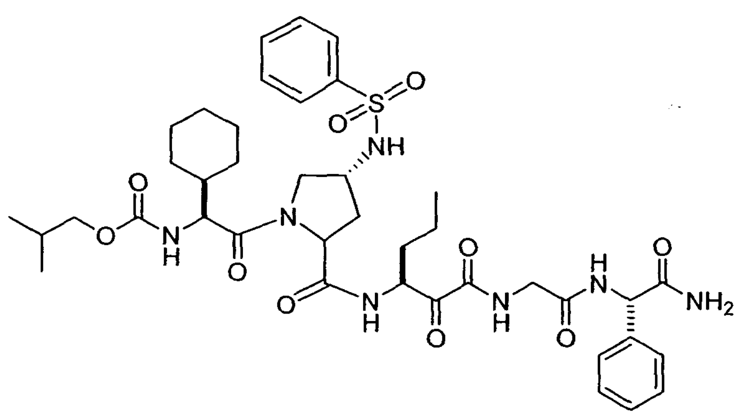
The resin obtained in the previous step (Fmoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction. To the resin (0.2 g, 0.22 mmol) suspended in 2 ml NMP was added isobutylchloroformate (0.12 ml, 0.90 mmol) followed by diisopropylethylamine (0.31 ml, 1.79 mmol), and the reaction mixture was shaken for 18 hours at room temperature. Qualitative ninhydrin analysis showed colorless beads and solution indicating a successful reaction.

Step 9. Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(CO)-Gly-Phg-MBHA resin:



The compound of the previous step (iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) (200 mg) was subjected to semicarbazone hydrolysis Procedure D.

Step 10. Synthesis of Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(CO)-Gly-Phg-NH_2:



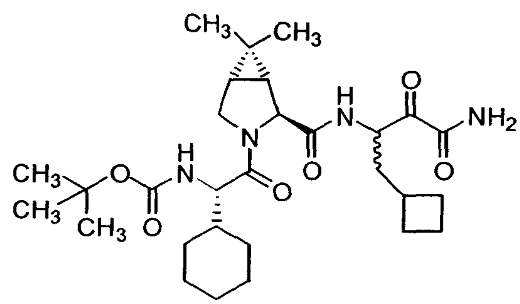
The resin of the previous step (iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(CO)-Gly-Phg-MBHA resin) (100 mg) was subjected to HF cleavage condition (Procedure E) to yield the desired crude product. The material was purified by HPLC using a 2.2 × 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting

with a gradient using 20-50% acetonitrile in water. Analytical HPLC using a 4.6 × 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 25-75% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 13.5 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 826.4).

IV. Additional Compounds Prepared by Solution Phase Synthesis:

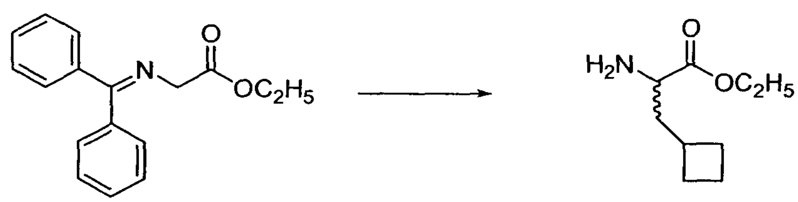
Representative procedures to prepare additional inventive compounds are shown below, and the compounds prepared by such procedures are listed in **Tables 5 and 6.**

Example XXIII : Preparation of a Compound of Formula XXIII:



XXIII

Step 1.

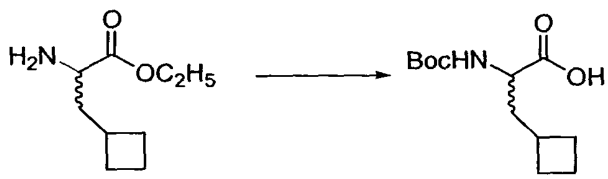


XXIIIa **XXXIIIb**

A stirred solution of ketimime **XXIIIa** (50 g, 187.1 mmol) under N_2 in dry THF (400 mL) was cooled to –78 ^{0}C and treated with 1 M solution of K-^{t}BuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0 ^{0}C and stirred for 1 h and treated with bromomethyl cyclobutane (28 mL, 249 mmol). The reaction

mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with aq. HCl (2 M, 300 mL) The resulting solution was stirred at room temperature for 5 h and extracted with Et_2O (1 L). The aqueous layer was made basic to pH ~12-14 with NaOH (50 % aq.) and extracted with CH_2Cl_2 (3x300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give pure amine (**XXIIIb**, 18 g) as a colorless oil.

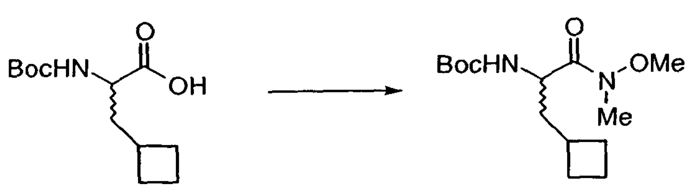
Step 2.



XXIIIb XXIIIc

A solution of amine **XXIIIb** (18g, 105.2 mmol) at 0 ^{0}C in CH_2Cl_2 (350 mL) was treated with di-*tert*-butyldicarbonate (23 g, 105.4 mmol) and stirred at rt. for 12 h. After the completion of the reaction (TLC), the reaction mixture was concentrated in *vacuo* and the residue was dissolved in THF/H_2O (200 ml, 1:1) and treated with LiOH•H_2O (6.5 g, 158.5 mmol) and stirred at room temperature for 3 h. The reaction mixture was concentrated and the basic aqueous layer was extracted with Et_2O. The aqueous layer was acidified with conc. HCl to pH~1-2 and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo* to yield **XXIIIc** as a colorless viscous oil which was used for next step without any further purification.

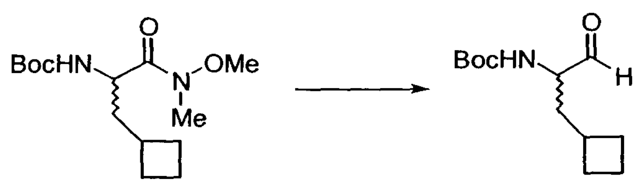
Step 3.



XXIIIc **XXIIId**

A solution of acid **XXIIIc** (15.0 g, 62 mmol) in CH_2Cl_2 (250 mL) was treated with BOP reagent (41.1 g, 93 mmol), N-methyl morpholine (27 mL), N,O-dimethyl hydroxylamine hydrochloride (9.07 g, 93 mmol) and stirred overnight at rt. The reaction mixture was diluted with 1 N aq. HCl (250 mL), and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x300 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield the amide **XXIIId** (15.0 g) as a colorless solid.

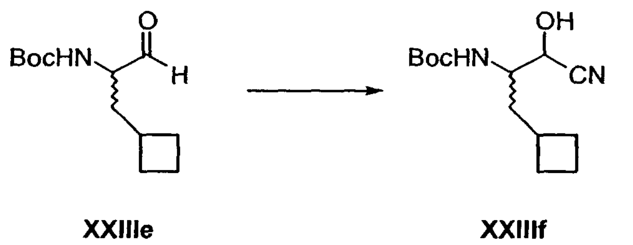
Step 4.



XXIIId **XXIIIe**

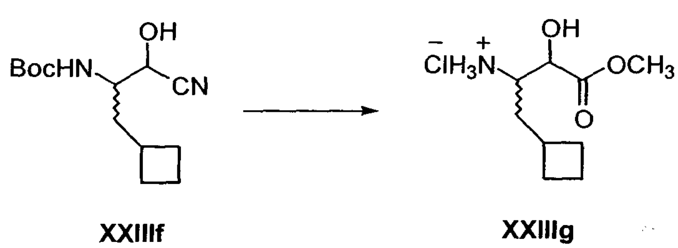
A solution of amide **XXIIId** (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwisely with a solution of $LiAlH_4$ (1M, 93 mL, 93 mmol) at 0 ^{0}C. The reaction mixture was stirred at room temperature for 1 h and carefully quenched at 0 °C with a solution of $KHSO_4$ (10% aq.) and stirred for 0.5 h. The reaction mixture was diluted with aq. HCl (1 M, 150 mL) and extracted with CH_2Cl_2 (3x200 mL), The combined organic layers were washed with aq. HCl (1 M), saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated in *vacuo* to yield **XXIIIe** as a viscous colorless oil (14 g).

Step 5.



A solution of the aldehyde **XXIIIe** (14 g, 61.6 mmol) in CH_2Cl_2 (50 mL), was treated with Et_3N (10.73 mL, 74.4 mmol), and acetone cyanohydrin (10.86 g, 127.57 mmol) and stirred at room temperature for 24 hrs. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (1 M, 200 mL) and extracted into CH_2Cl_2 (3x200 mL). The combined organic layer were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:4) to yield **XXIIIf** (10.3 g) as a colorless liquid

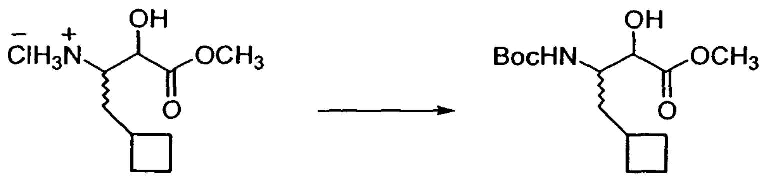
Step 6.



Methanol saturated with HCl*, prepared by bubbling HCl gas to CH_3OH (700 ml) at 0 °C, was treated with cyanohydrin **XXIIIf** and heated to reflux for 24 h. The reaction was concentrated in *vacuo* to yield **XXIIIg**, which was used in the next step without purification.

* Alternatively 6M HCl prepared by addition of AcCl to dry methanol can also be used.

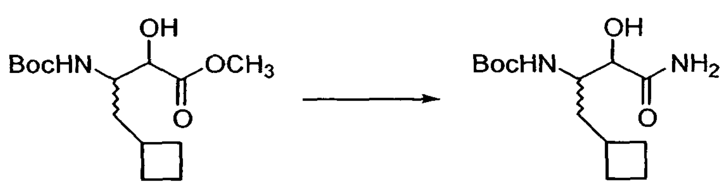
Step 7.



XXIIIg XXIIIh

A solution of the amine hydrochloride **XXIIIg** in CH_2Cl_2 (200 mL) was treated with Et_3N (45.0 mL, 315 mmol) and Boc_2O (45.7g, 209 mmol) at –78 °C. The reaction mixture was then stirred at room temperature overnight and diluted with HCl (2 M, 200 mL) and extracted into CH_2Cl_2. The combined organic layer were dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (EtOAc/Hex 1:4) to yield hydroxy ester **XXIIIh**.

Step 8.



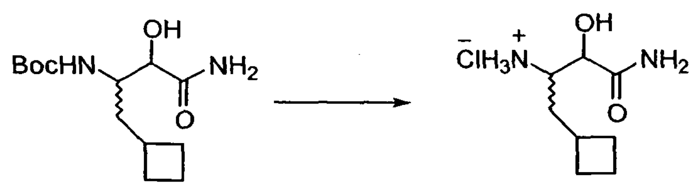
XXIIIh XXIIIi

A solution of methyl ester **XXIIIh** (3g, 10.5 mmol) in THF/H_2O (1:1) was treated with LiOH•H_2O (645 mg, 15.75 mmol) and stirred at rt. for 2 h. The reaction mixture was acidfied with aq HCl (1 M, 15 mL) and concentrated in *vacuo*. The residue was dried in vacuum.

A solution of the acid in CH_2Cl_2 (50 mL) and DMF (25 mL) was treated with NH_4Cl (2.94 g, 55.5 mmol), EDCI (3.15 g, 16.5 mmol), HOOBt (2.69 g, 16.5 mmol), and NMM (4.4 g, 44 mmol). The reaction mixture was stirred at room temperature for 3 d. The solvents were removed under *vacuo* and the residue was diluted with aq. HCl (250 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. Sat'd. $NaHCO_3$, dried ($MgSO_4$) filtered concentrated

in vacuo to obtain **XXIIIi**, which was used as it is in the following steps. (Alternatively **XXIIIi** can also be obtained directly by the reaction of **XXIIIf** (4.5 g, 17.7 mmol) with aq. H_2O_2 (10 mL), $LiOH{\bullet}H_2O$ (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.)

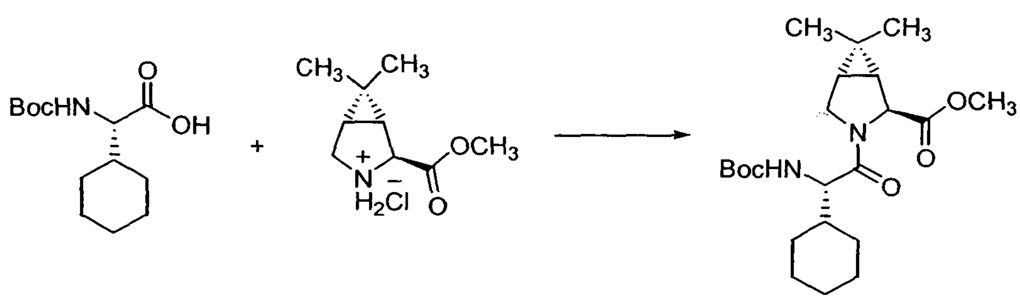
Step 9.



XXIIIi XXIIIj

A solution of **XXIIIi** obtained in the previous step was dissolved in 4 N HCl in dioxane and stirred at rt. for 2 h. The reaction mixture was concentrated in *vacuo* to give **XXIIIj** as a solid, which was used without further purification.

Step 10.

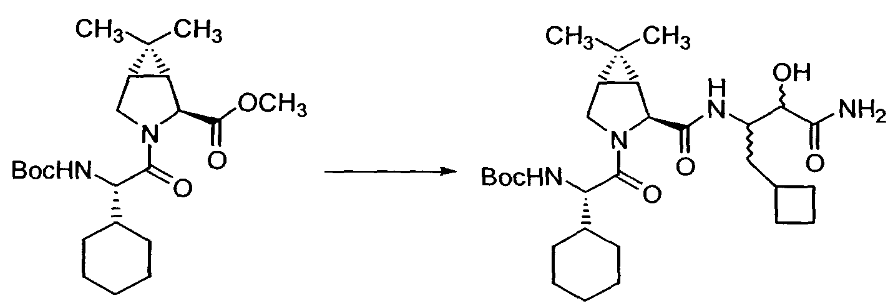


XXIIIk XXIIIl XXIIIm

The amino ester **XXIIIl** was prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), with the exeception that the Boc group was cleved by the reaction of the Boc-protected amino acid with methanolic HCl.

A solution of commercial amino acid Boc-Chg-OH, **XXIIIk** (Senn chemicals, 6.64 g, 24.1 mmol) and amine hydrochloride **XXIIIl** (4.5 g, 22 mmol) in CH_2Cl_2 (100 mL) at 0 °C was treated with BOP reagent and stirred at rt. for 15 h. The reaction mixture was concentrated *in vacuo*, then it was diluted with aq. 1 M HCl and extracted into EtOAc (3x200 mL). The combined organic layers were washed with sat'd. $NaHCO_3$ (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, and chromatographed (SiO_2, EtOAc/Hex 3:7) to obtain **XXIIIm** (6.0 g) as a colorless solid.

Step 11.

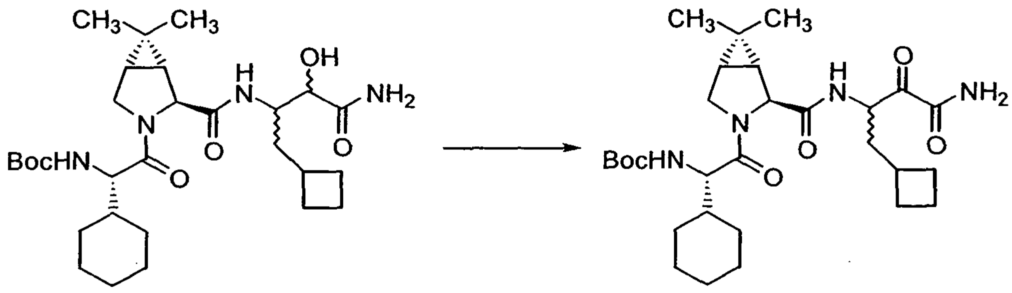


XXIIIm **XXIIIn**

A solution of methyl ester **XXIIIm** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with LiOH•H_2O (401 mg, 9.79 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (1.5 g, 3.74 mmol) in DMF/CH_2Cl_2 (1:1 50mL) was treated with amine **XXIIIj** (772 mg, 3.74 mmol), EDCI (1.07 g, 5.61 mmol), HOOBt (959 mg , 5.61 mmol) and NMM (2.15 mL, 14.96 mmol) at -10 °C. The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl and extracted with CH_2Cl_2, The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$), filtered and concentrated in vacuo to obtain **XXIIIn** (2.08 g) as a tan colored solid.

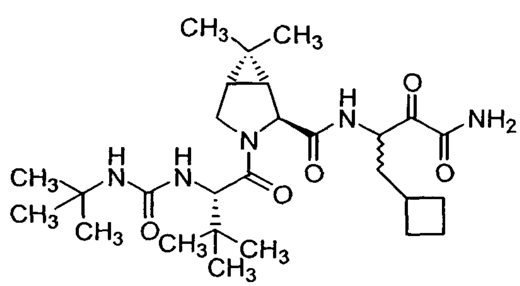
Step12.



XXIIIn XXIII

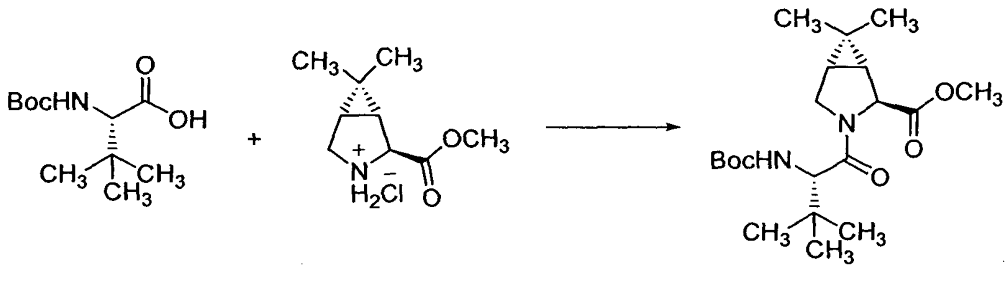
A solution of amide **XXIIIn** (2.08 g, 3.79 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (7.24 g, 37.9 mmol) and dichloroacetic acid (2.42 g, 19.9 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with sat'd. $NaHCO_3$, and brine. The organic layer were dried ($MgSO_4$) filtered, concentrated, in vacuo and purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield **XXIII** as a colorless solid.

Example XXIV Preparation of a Compound of Formula XXIV:



XXIV

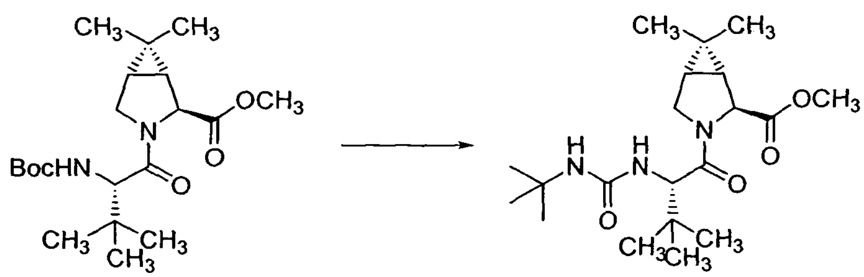
Step 1.



XXIVa **XXIIII** **XXIVb**

A solution of Boc-tert-Lue **XXIVa** (Fluka, 5.0 g 21.6 mmol) in dry CH_2Cl_2/DMF (50 mL, 1:1) was cooled to 0 °C and treated with the amine **XXIIII** (5.3 g, 25.7 mmol), NMM (6.5 g, 64.8 mmol) and BOP reagent (11.6 g, 25.7 mmol). The reaction was stirred at rt. for 24h, diluted with aq. HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were washed with HCL (aq, 1 M), sat'd. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo and purified by chromatography (SiO2, Acetone/Hexane 1:5) to yield **XXIVb** as a colorless solid.

Step 2.

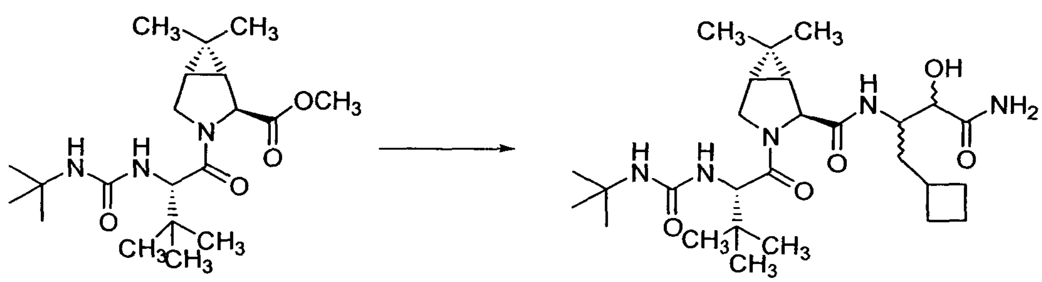


XXIVb **XXIVc**

A solution of methyl ester **XXIVb** (4.0 g, 10.46 mmol) was dissolved in HCl (4 M soln. dioxane) and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* to obtain the amine hydrochloride salt used in the next step.

A solution of the amine hydrochloride salt (397 mg, 1.24 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and treated with *tert*-butyl isocyanate (250 mg, 2.5 mmol) and stirred at rt. overnight. The reaction mixture was concentrated in vacuo and the residue was diluted with aq. HCl (1M) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. HCl (1M), sat'd. $NaHCO_3$ and brine. The organic layers were dried, filtered and concentrated in vacuo and the residue was purified by chromatography (SiO_2, acetone/Hex 1:4) to yield **XXIVc** as a colorless solid.

<u>Step 3</u>.

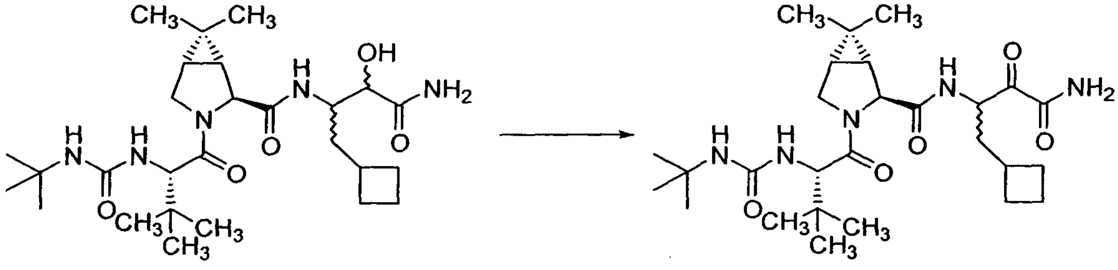


XXIVc XXIVd

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with LiOH•H_2O (62 mg, 1.5 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (254.9 mg, 0.69 mmol) in DMF/CH_2Cl_2 (1:1, 5.0 mL) was treated with amine **XXIIIj** (159 mg, 0.763 mmol), EDCI (199 mg, 1.04 mmol), HOOBt (169.5 mg , 1.04 mmol) and NMM (280 mg, 2.77 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 48 h and concentrated in *vacuo*. The residue was diluted with aq. 1M HCl and extracted with EtOAc, The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* to obtain **XXIVd** (470 mg) as a tan colored solid.

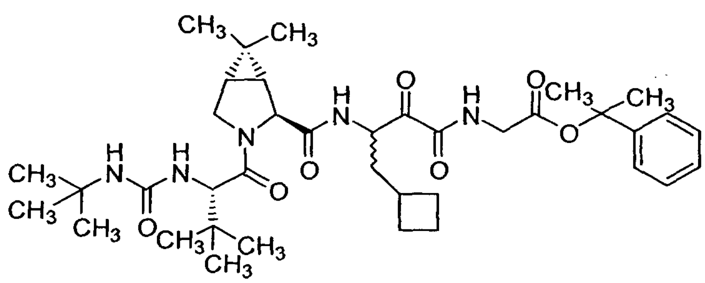
Step 4.



XXIVd XXIV

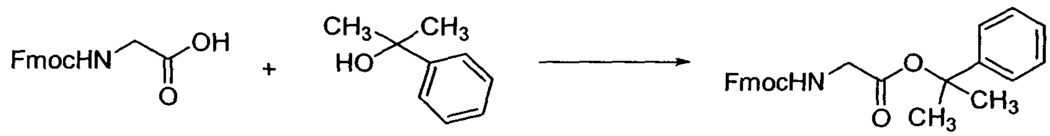
A solution of amide **XXIVd** (470 mg, 0.9 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (1.72 g, 9.0 mmol) and dichloroacetic acid (0.37 mL, 4.5 mmol) and stirred at 0 °C for 4h. The reaction mixture was diluted with CH_2Cl_2, and washed with satd. $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated, in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield **XXIV** as a colorless solid.

Example XXV Preparation of a compound of Formula XXV:



XXV

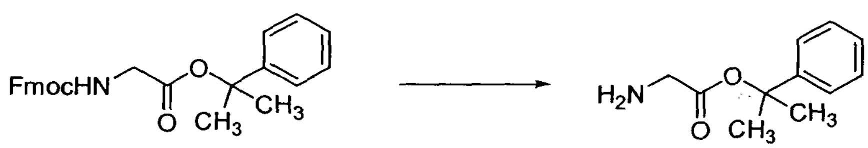
Step 1.



XXVa XXVb XXVc

A solution of Fmoc–glycine (Bachem, 2.0 g, 6.87 mmol) in CH_2Cl_2 (20 mL) was treated with 2-phenyl-2-propanol (Aldrich, 3.36 g, 24.7 mmol), DCC (1M soln CH_2Cl_2, 8.24 mL), DMAP (167 mg, 1.37 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with Et_2O (100 mL). The solid seperating out was filtered and the filterate was washed with satd. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by chromatography (SiO_2, EtOAc/Hex 1:5) to yield ester XXVc (1.1 g) as a colorless viscous liquid.

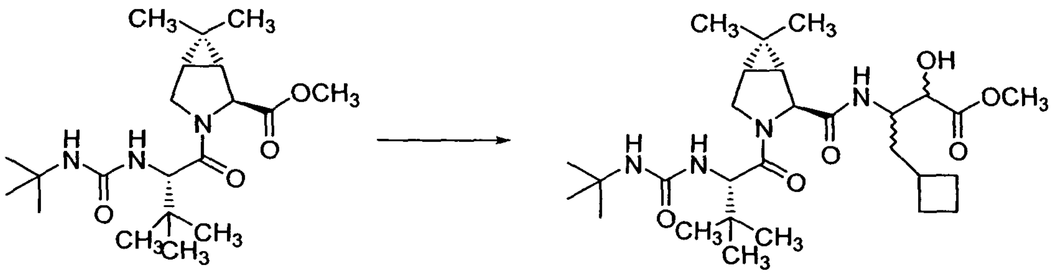
Step 2.



XXVc XXVd

A solution of XXVc in CH_2Cl_2 (16.0 mL) was treated with piperidine (4.0 mL) and stirred at rt. for 0.5 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 1:10 to 1:1) to yield the amine XXVd (420 mg) as a colorless liquid.

Step 3.

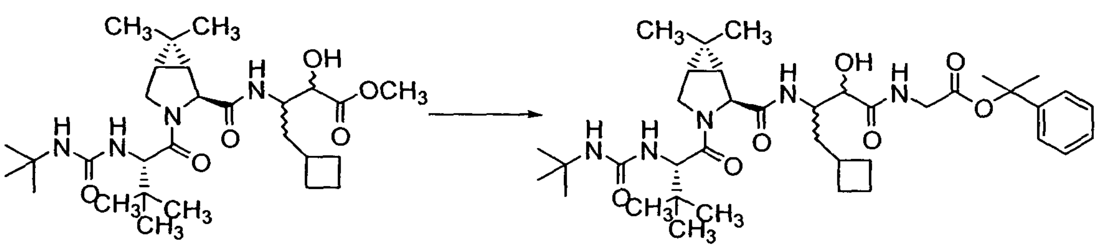


XXIVc XXVe

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with LiOH•H_2O (62 mg, 1.5 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (2.0 g, 5.5 mmol) in DMF/CH_2Cl_2 (1:1, 40.0 mL) at -10 °C was treated with amine XXIIIg (1.51 g, 6.8 mmol), EDCI (1.57 g, 8.25 mmol), HOOBt (1.41 g, 8.25 mmol) and NMM (2.5 g, 24.7 mmol). The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$) filtered, concentrated in *vacuo* to obtain XXVe (3.17 g) as a tan-colored solid used further without any purification.

Step 4.

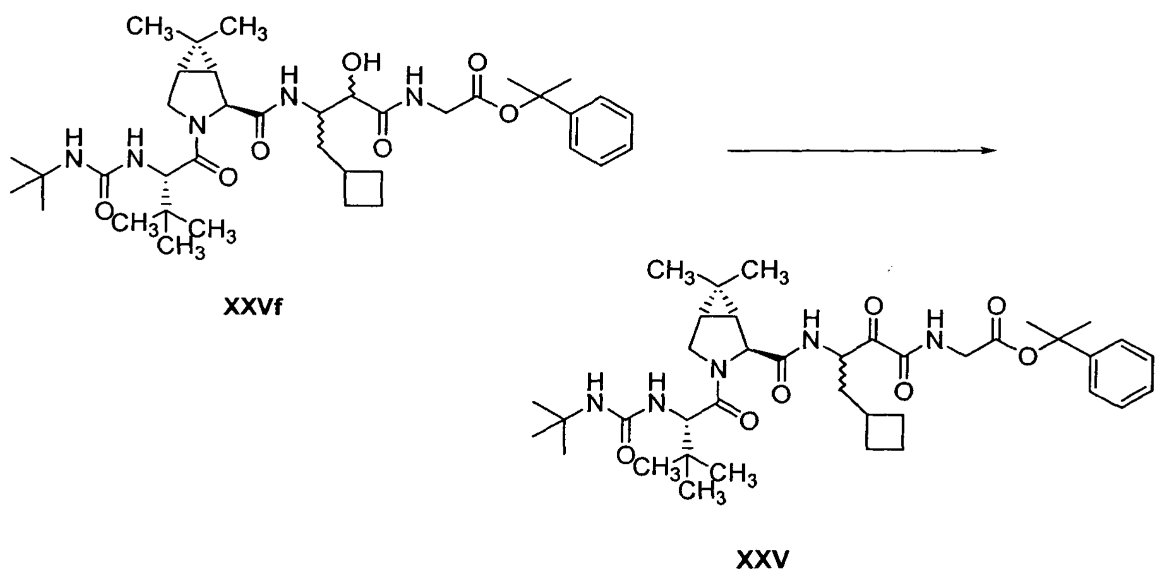


XXVe XXVf

A solution of methyl ester **XXVe** (2.5 g, 4.66 mmol) in $THF/H_2O/CH_3OH$ (1:1:1, 60 mL) was treated with $LiOH{\bullet}H_2O$ (200 mg, 4.87 mmol) and stirred at rt. for 4 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (200.0 mg, 0.38 mmol) in DMF/CH_2Cl_2 (1:1, 6.0 mL) at -10 °C was treated with amine XXVd (78 mg, 0.4 mmol), EDCI (105 mg, 0.55 mmol), HOOBt (95 mg, 0.55 mmol) and NMM (150 mg, 1.48 mmol). The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl (30 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with aq. $NaHCO_3$ (2x30 mL), aq. HCl, brine (30 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* to obtain XXVf (240 mg) as a tan colored solid.

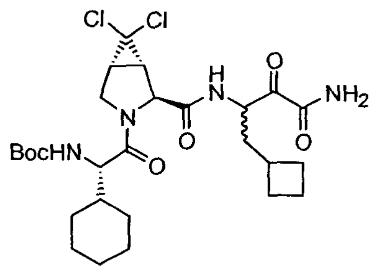
Step 5.



A solution of XXVf (240 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin reagent (Omega, 242 mg, 0.56 mmol) and stirred at rt. for 2 h. After the oxidation was complete (TLC, Acetone/Hex 1:4) the reaction mixture was diluted with satd. $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (10% aq soln, 20 mL). The

reaction mixture was stirred for 30 min and extractred with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with satd. NaHCO3, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1:5) to yield XXV (122 mg) as a colorless solid.

Example XXVI Preparation of a compound of Formula XXVI:



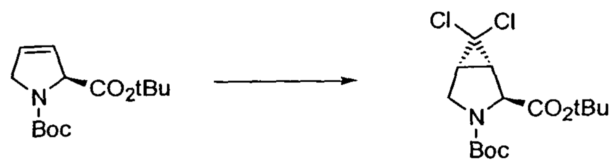
XXVI

Step 1:

XXVIa **XXVIb**

To a stirred solution of *N*-Boc-3,4-dehydroproline **XXVIa** (5.0 g, 23.5 mmol), di-*tert*-butyl dicarbonate (7.5 g, 34.4 mmol), and 4-*N,N*-dimethylaminopyridine (0.40 g, 3.33 mmol) in acetonitrile (100 mL) at room temperature was added triethylamine (5.0 mL, 35.6 mmol). The resulting solution was stirred at this temperature for 18 h before it was concentrated *in vacuo.* The dark brown residue was purified by flash column chromatography eluting with 10-25% EtOAc/hexane to give the product **XXVIb** as a pale yellow oil (5.29 g, 84%).

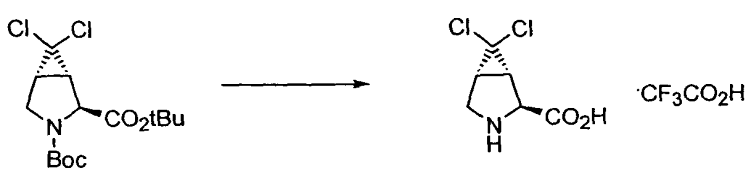
Step 2:



XXVIb XXVIc

To a stirred solution of dehydroproline **XXVIb** (10.1 g, 37.4 mmol), benzyltriethylammonium chloride (1.60 g, 7.02 mmol) in chloroform (120 mL) at room temperature was added 50% aqueous sodium hydroxide (120 g). After vigorously stirred at this temperature for 24 h, the black mixture was diluted with CH_2Cl_2 (200 mL) and diethyl ether (600 mL). After the layers were separated, the aqueous solution was extracted with CH_2Cl_2/Et_2O (1:2, 3x600 mL). The organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 9.34 g (71%) of **XXVIc** as an off-white solid.

Step 3:



XXVIc XXVId

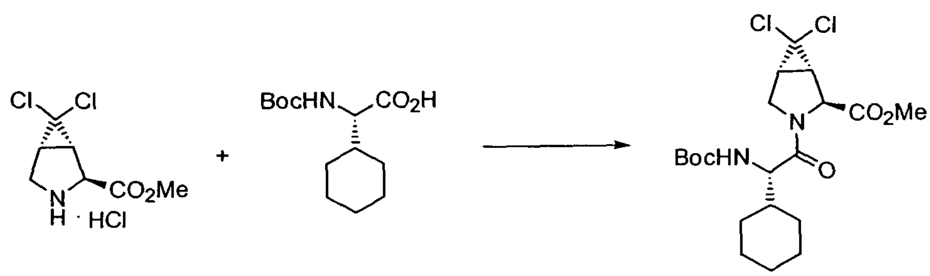
The solution of **XXVIc** (9.34 g, 26.5 mmol) in CH_2Cl_2 (25 mL) and CF_3CO_2H (50 mL) was stirred at room temperature for 4.5 h before it was concentrated *in vacuo* to give a brown residue which was used in Step 4 without further purification.

Step 4

XXIIId XXIIIe

Commercial concentrated hydrochloric acid (4.5 mL) was added to a solution of the residue from Step 3 in methanol (70 mL) and the resulting mixture was warmed to 65°C in an oil bath. After 18 h, the mixture was concentrated *in vacuo* to give a brown oil **XXVIe**, which was used in Step 5 without further purification.

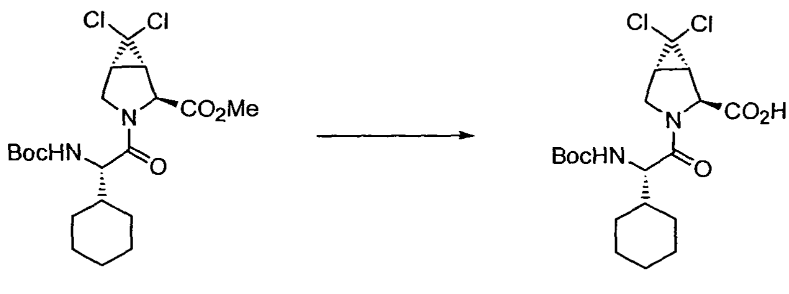
Step 5:



XXVIe XXVIf XXVIg

To a stirred solution of proline methyl ester **XXVIe** from Step 4, commercial N-Boc-cyclohexylglycine **XXVIf** (10.2 g, 40.0 mmol) and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) (16.0 g, 42.1 mmol) in DMF (200 mL) at 0°C was added diisopropylethylamine (18.0 mL, 104 mmol). After allowed to warm to room temperature along with the ice bath over night (18 h), the reaction mixture was diluted with EtOAc (600 mL), 5% H_3PO_4 (150 mL) and brine (150 mL). The organic solution was washed with 5% H_3PO_4 (150 mL), saturated $NaHCO_3$ (2x200 mL) before it was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 3.84 g (32%, three steps) of **XXVIg** as an off-white solid.

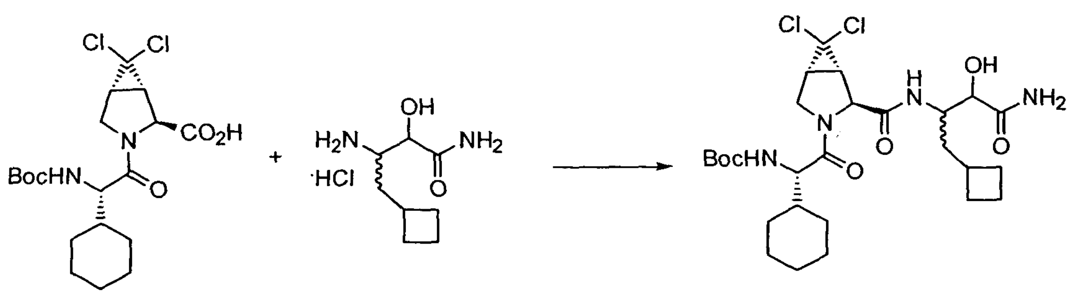
Step 6:



XXVIg XXVIh

The solution of methyl ester **XXVIg** (5.87g, 13.1 mmol) and LiOH (1.65 g, 39.3 mmol) in THF/MeOH/H_2O (1:1:1, 90 mL) was stirred at room temperature for 4 h. Methanol and THF were removed under reduced pressure. The aqueous solution was acidified to PH~2 using 1 N aqueous HCl solution (50 mL) and saturated with solid sodium chloride before it was extracted with EtOAc (3x150 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid **XXVIh** (5.8 g, quantitative).

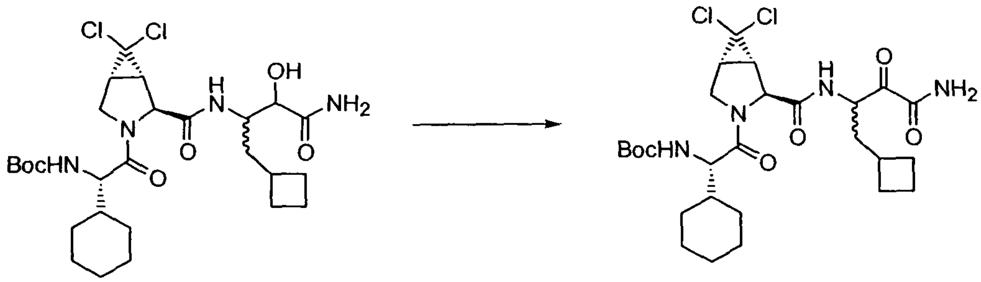
Step 7:



XXVIh XXIIIj XXVIi

The desired product **XXIIIi** was prepared according to the procedure in Example XXIII, Step 11.

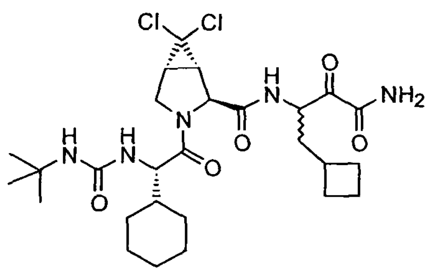
Step 8:



XXVIi XXVI

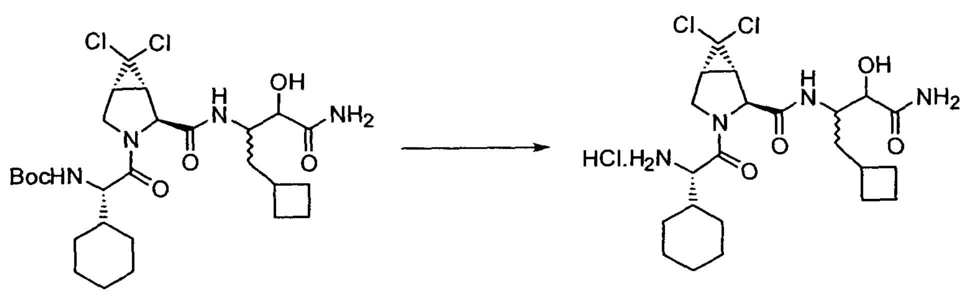
The desired product **XXVI** was prepared according to the procedure in Example XXIII, Step 12.

Example XXVII: Preparation of compound of formula XXVII:



XXVII

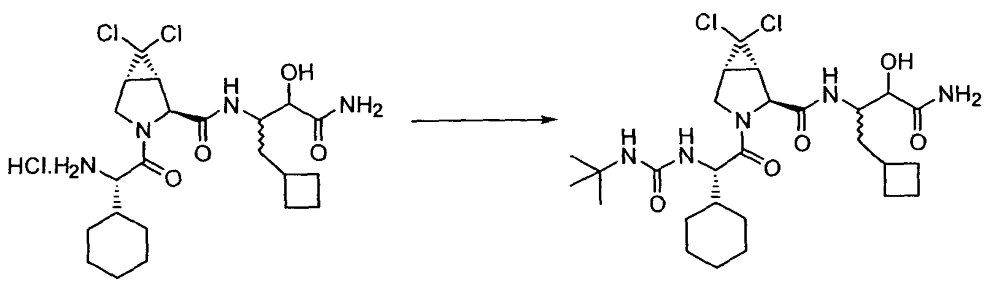
Step 1



XXVIi XXVIIa

The desired product **XXVIIa** was prepared according to the procedure in Example XXIII, Step 9.

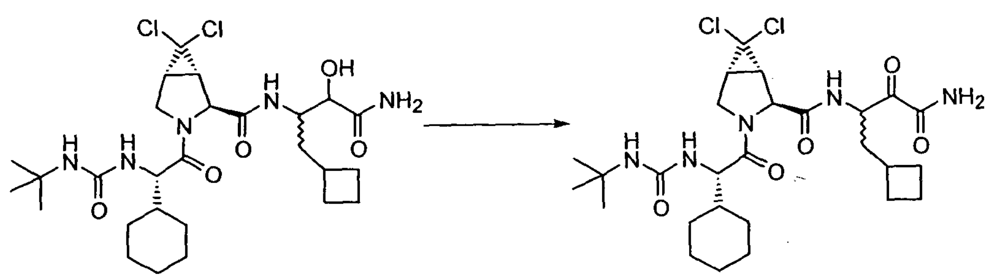
Step 2



XXVIIa **XXVIIb**

The desired product **XXVIIb** was prepared according to the procedure in Example XXIV, Step 2.

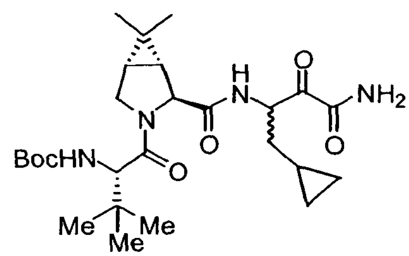
Step 3



XXVIIb **XXVII**

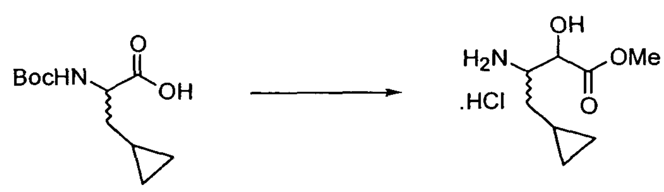
The desired product **XXVII** was prepared according to the procedure in Example XXIII, Step 12.

Example XXVIII: Preparation of a compound of formula XXVIII:



XXVIII

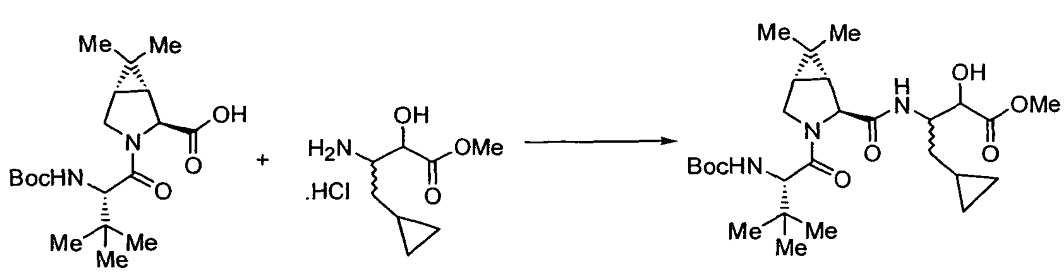
<u>Step 1:</u>



XXVIIIa **XXVIIIb**

The intermediate **XXVIIIb** was prepared according to the procedure in Example XXIII, Steps 3-6.

<u>Step 2:</u>

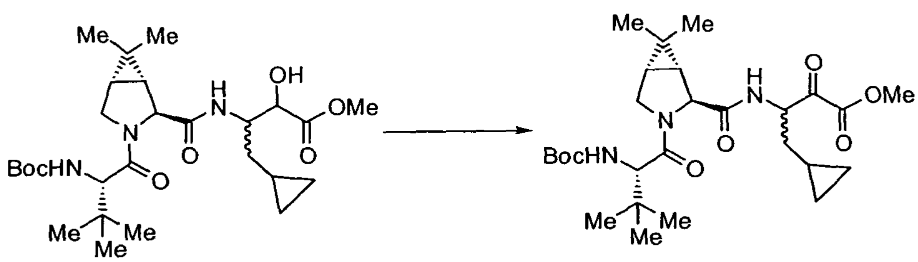


XXVIIIc **XXVIIIb** **XXVIIId**

The acid from Example XXIV, Step 2 (**XXVIIIc**) (0.7g) was reacted with product from Step 1 above (0.436g), HATU (0.934g) and DIPEA (1.64 mL) in the

manner previously described in Example IX, Step 2a to afford 0.66 g of the desired product **XXVIIId.**

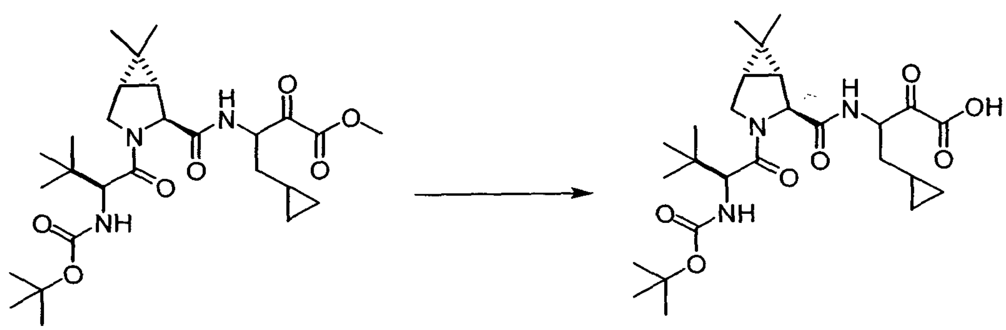
Step 3:



XXVIIId **XXVIIIe**

The product of Step 2 (0.5g) was reacted with Dess-Martin reagent (1g) in the manner previously described in Example XX, Step 7. Purification by flash column chromatography (40% EtOAc, Hexane, silica) furnished 0.35g of product **XXVIIIe**. Mass spectrum (LCMS) 522 ($M+H^+$).

Step 4:

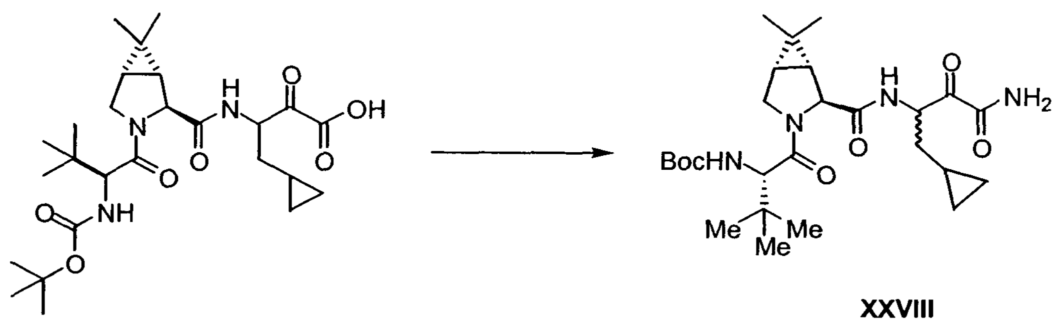


XXVIIIe **XXVIIIf**

The product of Step 4 (0.3g) was added a 1/1 H_2O/MeOH solution (20 mL) and NaHCO3 solid (242 mg, 5equiv.). After being stirred for 18 hours at room temperature, the reaction was diluted with EtOAc and layers were separated. The aqueous layer was acidified to pH 2 with HCl 1.0 N and extracted with EtOAc. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and

concentrated in vacuo to afford product **XXVIIIf** as a white powder (0.26g). Mass spectrum (LCMS) 508 ($M+H^+$).

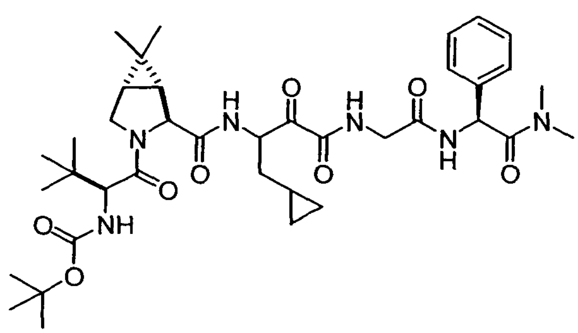
Step 5:



XXVIIIf XXVIII

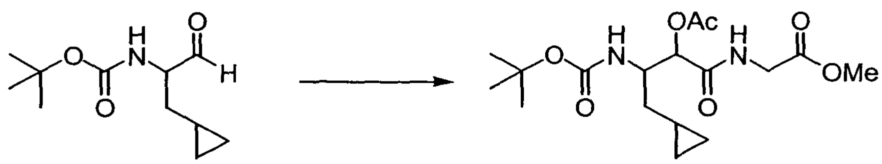
The product of Step 5 (0.15g) was dissolved in CH_2Cl_2 and reacted with HATU (0.137g), NH_4Cl (0.08g, 5equiv.) and DIPEA (0.53 mL). After 2 hours at room temperature, the reaction was diluted with EtOAc, washed with a 10% citric acid solution, then a saturated $NaHCO_3$ solution. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (30% Acetone, Hexane, silica) furnished the desired product **XXVIII** (0.096g). Mass spectrum (LCMS) 507 ($M+H^+$).

Example XXIX: Preparation of a compound of formula XXIX:



XXIX

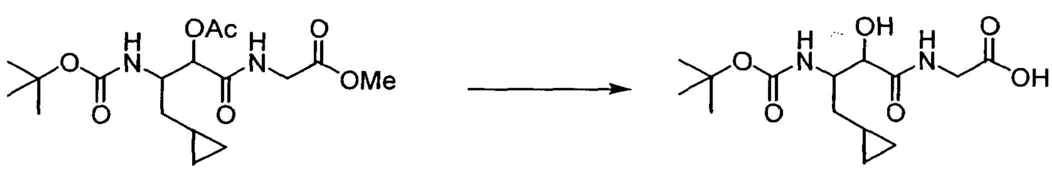
Step1:



XXIXa

To a 0 °C solution of the starting aldehyde (4.0g) in CH_2Cl_2 (75 mL) was added acetic acid (2.0 equiv., 2.15 mL) followed by methylisocyanoacetate (1.1 equiv., 1.9 mL). The reaction was then gradually warmed-up to room temperature. After 18 hours (overnight), the reaction was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (30 to 40% EtOAc, Hexane, silica) furnished the product **XXIXa** (4.5g).

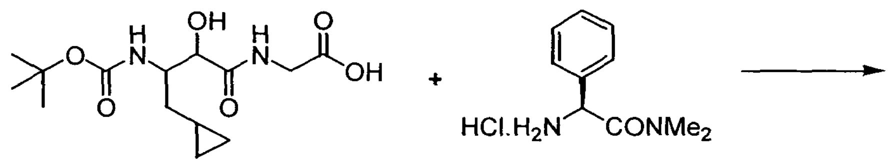
Step2:



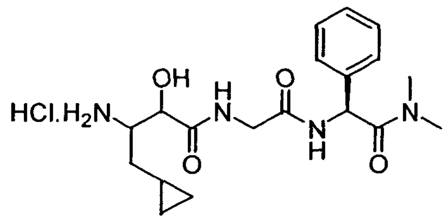
XXIXa XXIXb

To a 0 °C solution of **XXIXa** (4.4g) in THF (100 mL) was added 26 mL (2.2 equiv.) of a 1.0 N LiOH solution. The reaction was stirred at this temperature for 2 hours then warmed-up to room temperature. After 2 hours, reaction mixture was acidified to pH 2 with a 1.0 N HCl solution. EtOAc was added and layers were separated. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford product **XXIXb** (3.7g).

Step3:



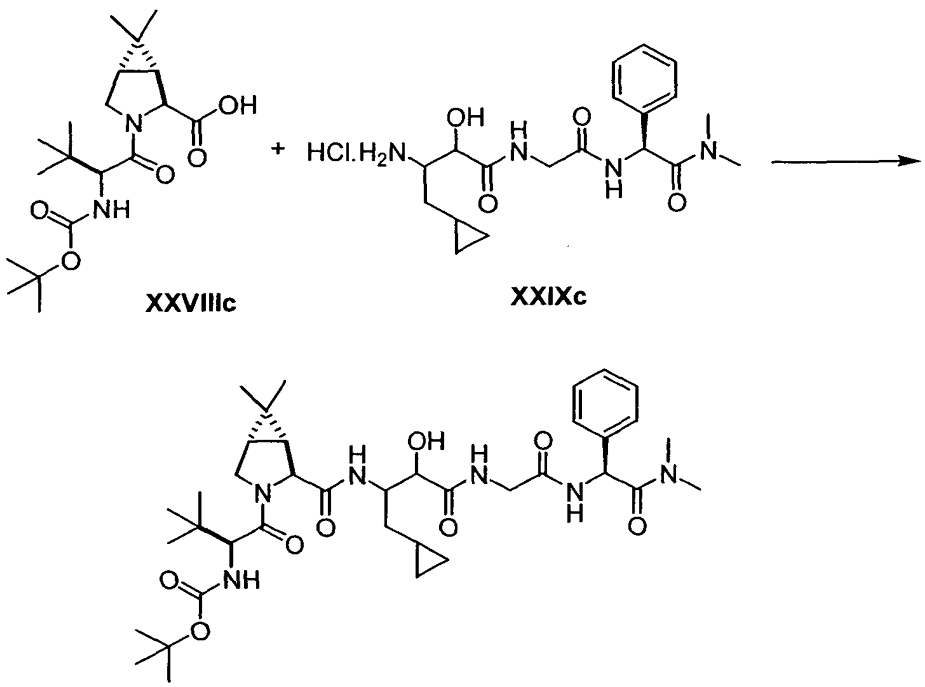
XXIXb **XV**



XXIXc

The acid **XXIXb** was reacted with the amine from Example XV in the manner previously described in Example XXI, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example XXIII, Step 9 to afford product **XXIXc**.

Step4:

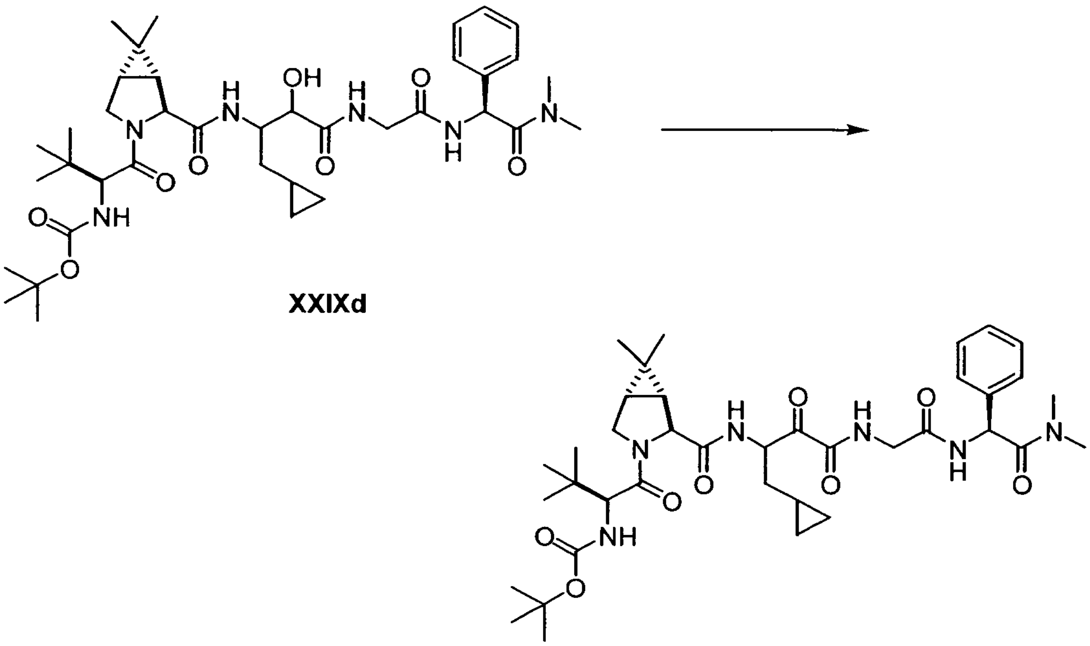


XXVIIIc XXIXc

XXIXd

The acid **XXVIIIc** (2.43g) was dissolved in CH_2Cl_2 and was reacted with amine **XXIXc** (2.47g), HATU (2.5g) and DIPEA (5.8 mL) in the manner previously described in Example IX, Step 2a to afford, after purification by flash column chromatography (4% MeOH, CH_2Cl_2, silica), the desired product **XXIXd** (4.35g). Mass spectrum (LCMS) 727 ($M+H^+$).

<u>Step 5:</u>

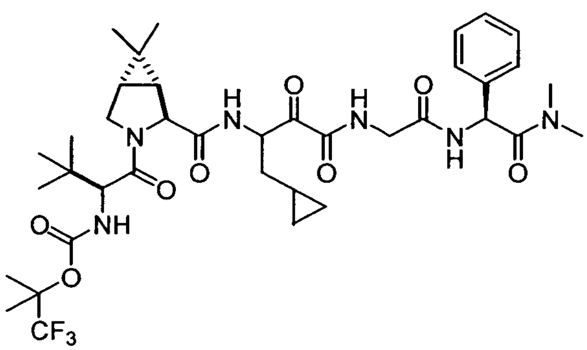


XXIXd

XXIX

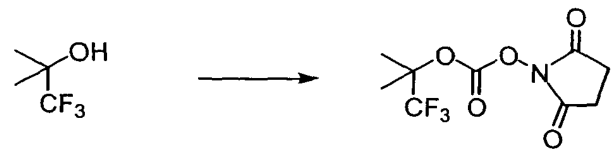
The product of Step 4 (4.2g) was reacted with Dess-Martin reagent (6.4g) in the manner previously described in preparative Example XX, Step 7. Purification by flash column chromatography (100% EtOAc, silica) furnished 3 g of the final product **XXIX**. Mass spectrum (LCMS) 725 ($M+H^+$).

Example XXX: Preparation of a compound of formula XXX:



XXX

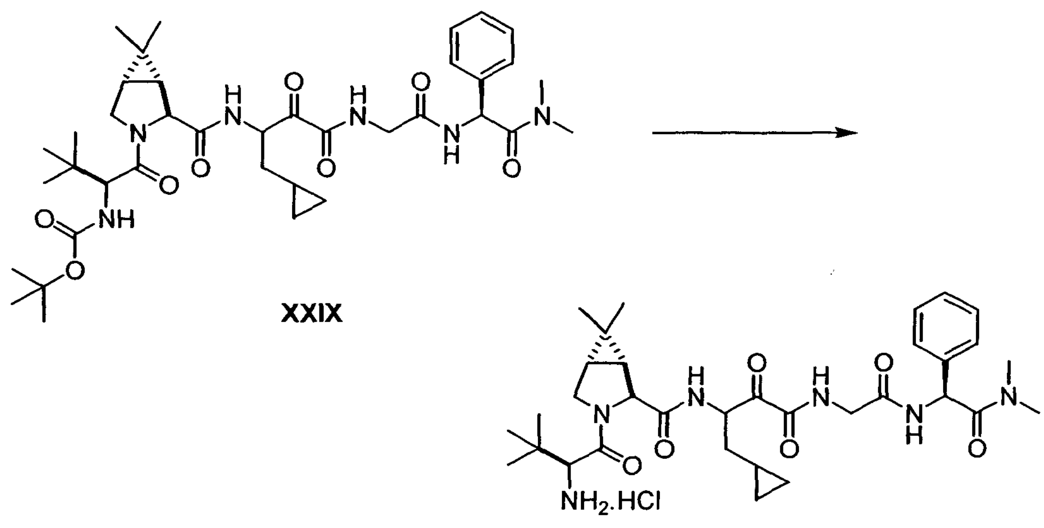
Step 1:



XXXa

The alcohol 2-(trifluoromethyl)propan-2-ol (1.28g) was reacted with N,N-disucciminidyl carbonate (3.84g) and Et_3N (4.2 mL) in dry CH_3CN (50 mL) for 18 hours. The mixture was diluted with EtOAc (200 mL) and filtered. The filtrate was washed with $NaHCO_3$, brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (50% EtOAc, Hexane, silica) furnished the desired product **XXXa** (0.3g).

Step 2:



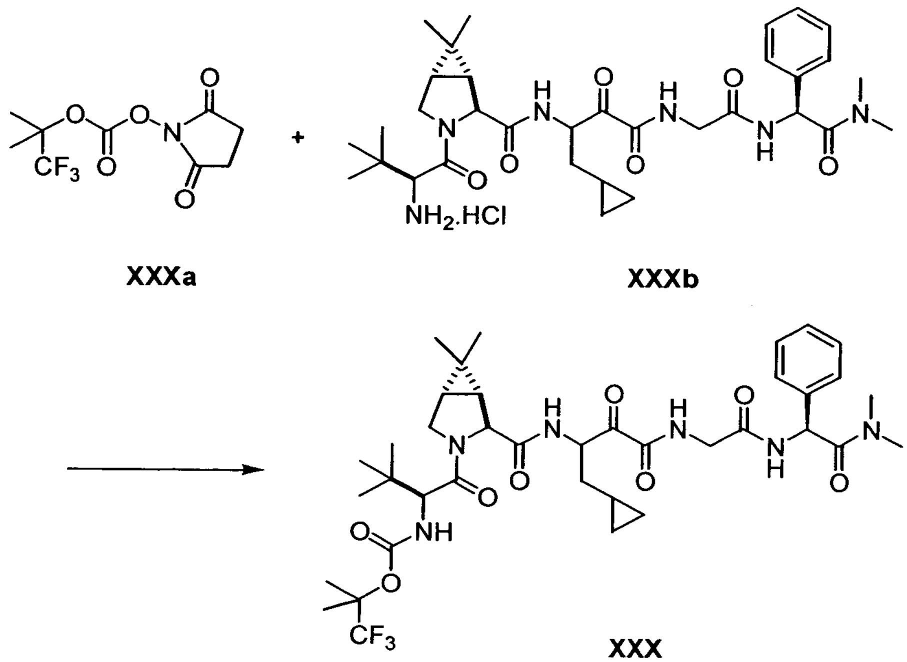
XXIX

XXXb

The product from Example XXIX (0.3g) was treated with 100 mL of 4.0 N HCl in dioxane. After 1 h, 200 mL of Et_2O were added and the resulting precipitate

was filtered off and dried under vacuo to afford the product **XXXb** (0.27g) as a white powder. Mass spectrum (LCMS) 625 (M – HCl +H^+).

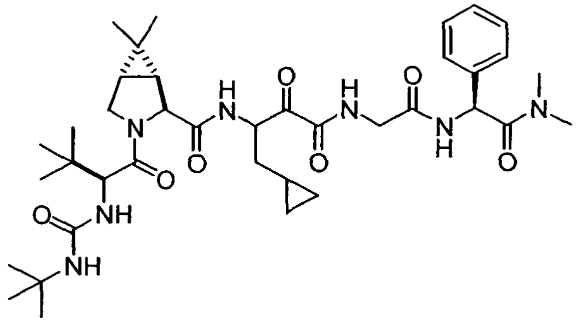
<u>Step 3:</u>



XXXa XXXb XXX

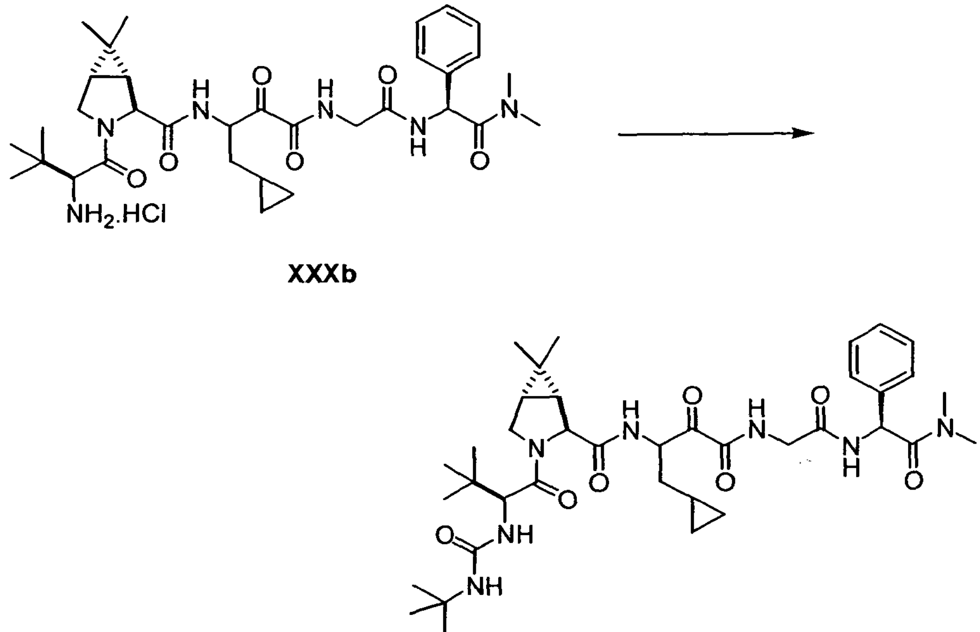
To a room temperature solution of **XXXb** (0.05g) in CH_2Cl_2 (5 mL) was added DIPEA (0.040 mL) **XXXa** (1.5 equiv., 0.030g), followed by 1 crystal of DMAP. After 30 minutes, reaction was diluted with EtOAc (20 mL) and washed with HCl 1.5 N then $NaHCO_3$ then brine. EtOAc layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by preparative chromatography (40% Acetone, Hexane, silica) furnished the desired product **XXX** (0.044g). Mass spectrum (LCMS) 779 (M+H^+).

<u>Example XXXI: Preparation of a compound of formula XXXI:</u>



XXXI

Step 1:



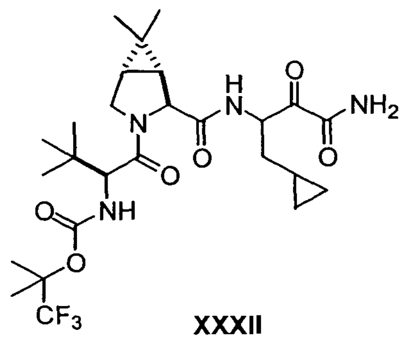
XXXb

XXXI

To a solution of **XXXb** (0.05g) in CH_2Cl_2 (5 mL) at room temperature was added DIPEA (0.040 mL) and *tert*-butylisocyanate (1.2 equiv., 0.01 mL). After 18 hours, reaction was diluted with EtOAc (20 mL) and washed with HCl 1.5 N, $NaHCO_3$ and brine. EtOAc layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by preparative chromatography

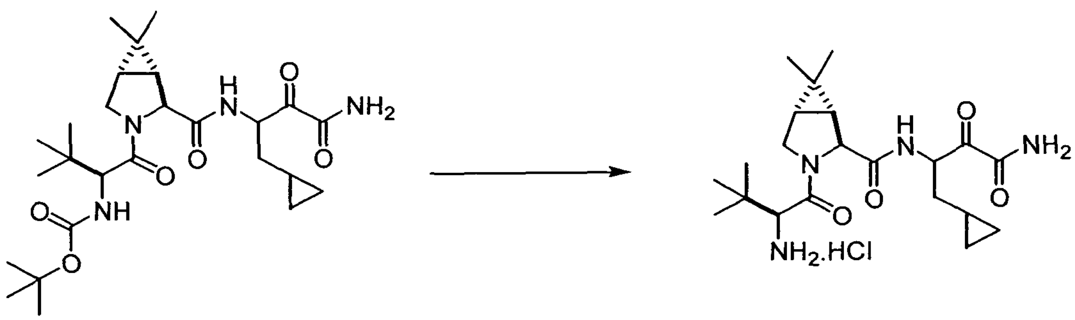
(100% EtOAc, silica) furnished the final product **XXXI** (0.021g). Mass spectrum (LCMS) 724 (M+H$^+$).

Example XXXII: Preparation of a compound of formula XXXII:



XXXII

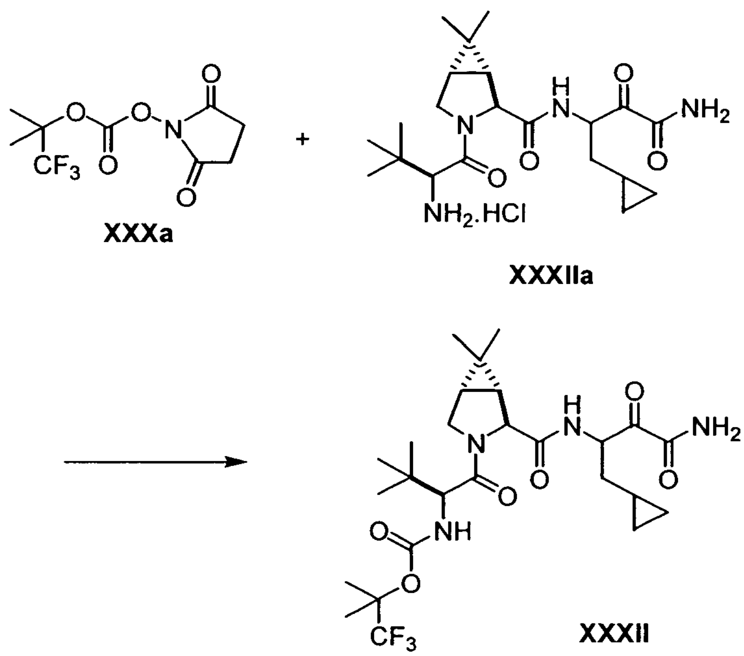
Step 1:



XXVIII **XXXIIa**

The product from Example XXVIII was treated in the manner previously described in preparative Example XXX, Step 2 to afford product **XXXIIa**. Mass spectrum (LCMS) 407 (M – HCl +H$^+$).

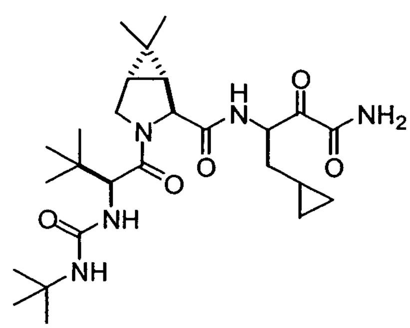
Step 2:



XXXa XXXIIa XXXII

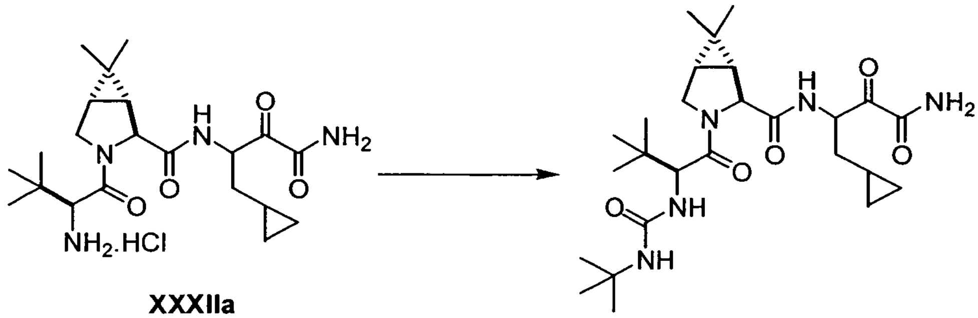
The amine **XXXIIa** was reacted with **XXXa** in the manner previously described in preparative Example XXX, Step 3 to afford the desired product **XXXII**. Mass spectrum (LCMS) 508 ($M+H^+$).

<u>Example XXXIII: Preparation of a compound of formula XXXIII:</u>



XXXIII

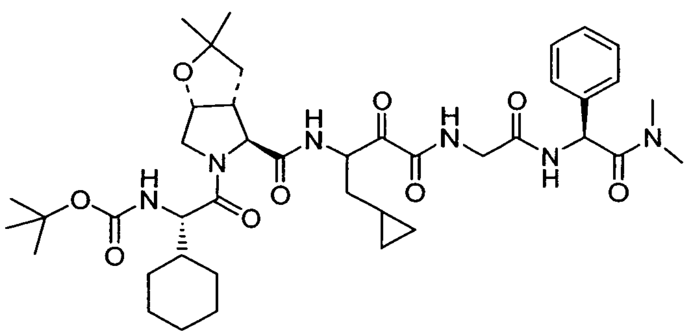
<u>Step 1:</u>



XXXIIa XXXIII

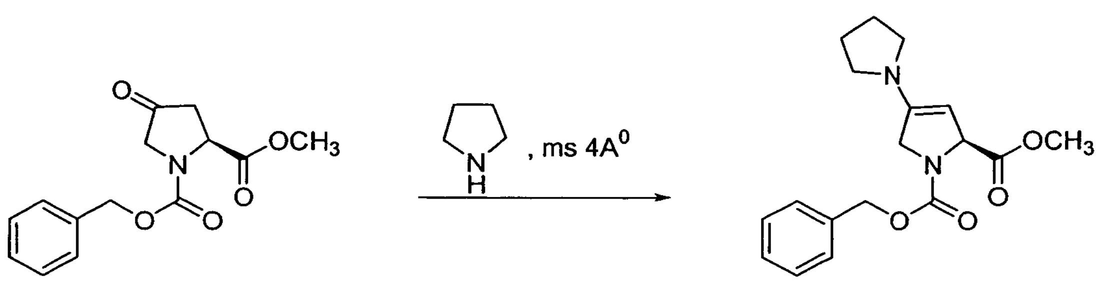
The amine **XXXIIa** was reacted with *tert*-butylisocyanate in the manner previously described in Example XXXI, Step 1, to afford the product **XXXIII**. Mass spectrum (LCMS) 561 ($M+H^+$).

Example XXXIV: Preparation of a compound of formula XXXIV:



XXXIV

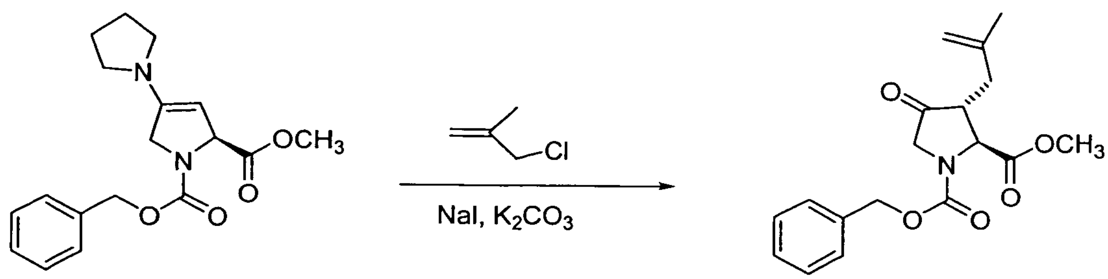
Step 1:



To the mixture of ester (6.0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was aded pyrrolidine (5.7 mL, 66.36 mmoL). The resulting brown slurry was stirred at room temperature under N_2 for 24 h, filtered

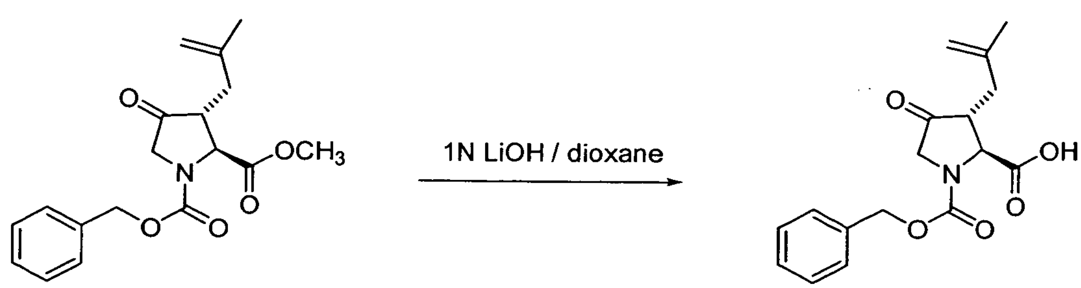
and washed with anhydrous CH_3CN. The combined filtrate was concentrated to yield the desired product.

Step 2:



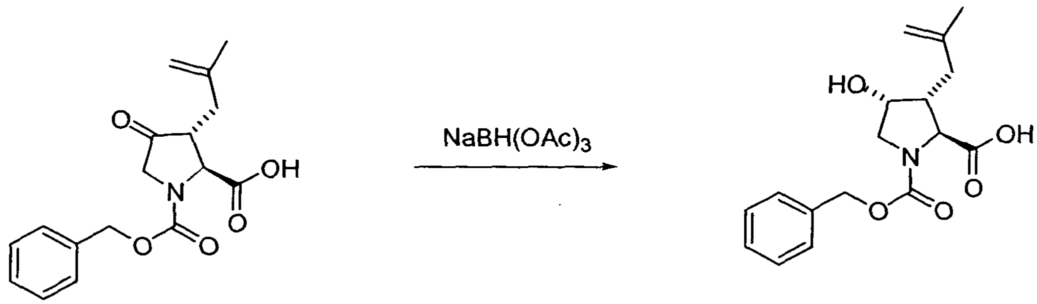
To a solution of the product from proceeding step in CH_3CN (35 mL) was added anhydrous K_2CO_3, methallyl chloride (2.77g, 30.5 mmoL), NaI (1.07g, 6.7 mmoL). The resulting slurry was stirred at ambient temperature under N_2 for 24 h. 50 mL of ice-cold water was added followed by 2N $KHSO_4$ solution until pH was 1. EtOAc (100 mL) was added and the mixture was stirred for 0.75h. Combined organic layer was collected and washed with brine, dried over $MgSO_4$, and evaporated to yield the desired product.

Step 3:



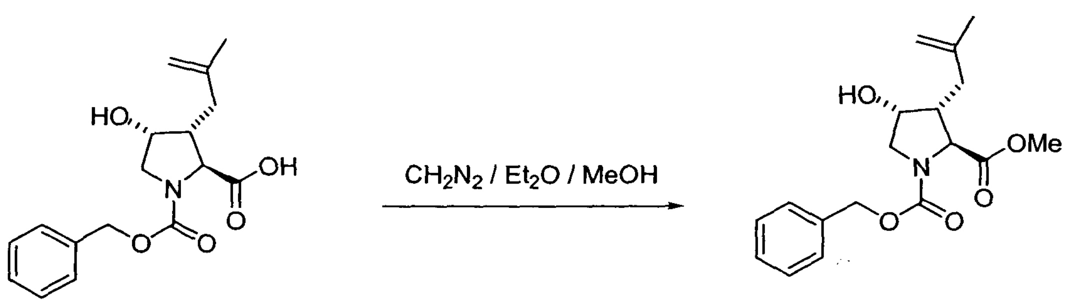
The product from preceding step (2.7 g, 8.16 mmoL) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL). The reaction mixture was stirred at ambient temperature under N_2 for 20 h. The reaction mixture was taken in EtOAc and washed with H_2O. The combined aqueous phase was cooled to 0^0C and acidifed to pH 1.65 using 1N HCl. The turbid mixture was extracted with EtOAc (2 x 100 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give the desired acid (3.40 g).

Step 4:



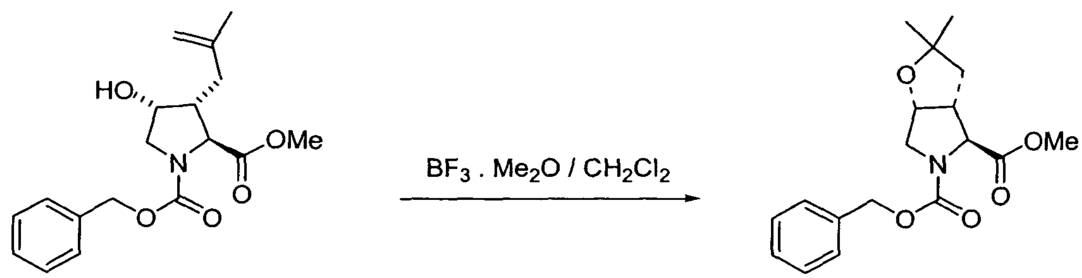
To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred for 1/2 hr. Organic layer was separated, filtered, dried and evaporated to yield the desired product.

Step 5:



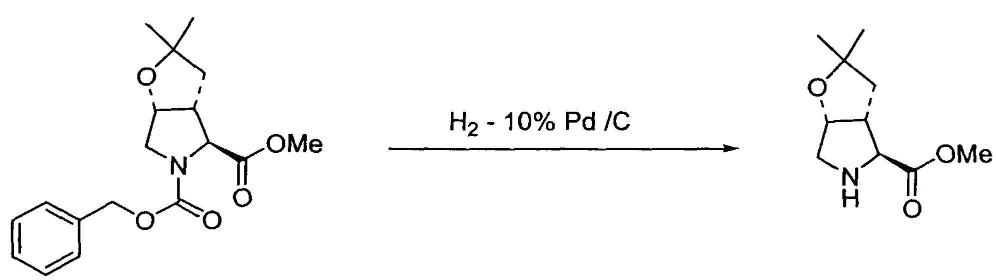
To a solution of the product from preceding step (1.9g) in MeOH (40 mL) was treated with excess of CH_2N_2 / Et_2O solution and stirred for overnight. The reaction mixture was concentrated to dryness to yield a crude residue. The residue was chromatographed on silica gel, eluting with a gradient of EtOAc / hexane to afford 1.07 g of the pure desired product.

Step 6:



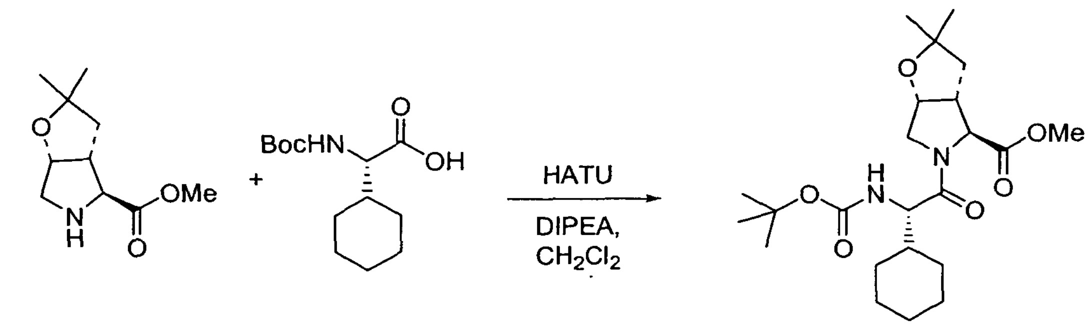
To a solution of product from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with BF_3. Me_2O (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched with sat. $NaHCO_3$ (30 mL) ad stirred for 1/2 hr. Organic layer was separated and combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give crude residue. The residue was chromotagraphed on silica gel eluting with a gradient of EtOAc / hexane to afford 0.88 g of the desired compound.

Step 7:



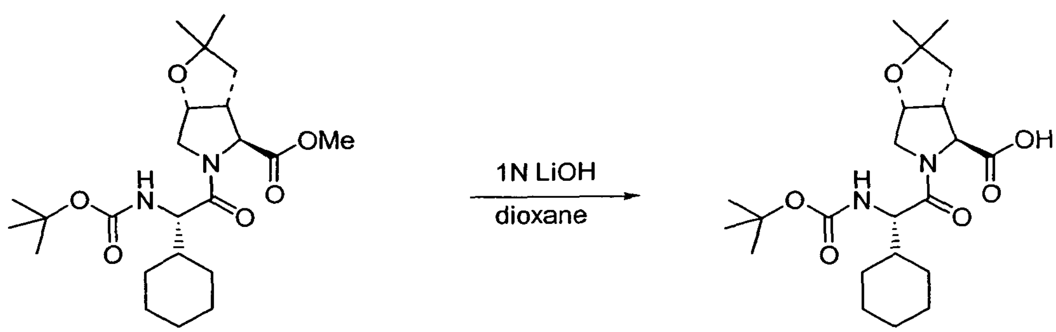
To a solution of the product (0.92 g) from preceding step in MeOH (30 mL) was added 10 % Pd/C (0.16 g) at room temperature and hydrogenated at ambient temperature under 1 atm. Pressure. The reaction mixture was stirred for 4 h and concentrated to dryness to yeild the desired compound.

Step 8:



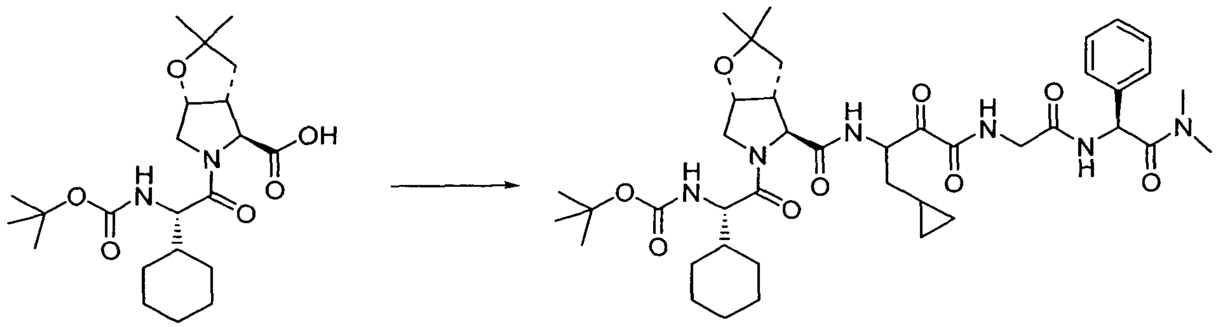
The desired product was prepared according to the procedure in Example XXIII, Step 10.

Step 9:



The desired acid product was prepared according to the procedure in Example XXIV, Step 3.

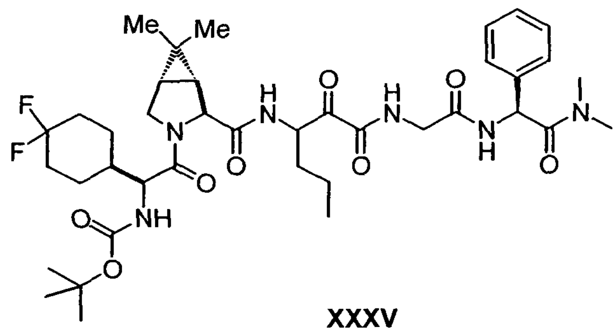
Step 10:



XXXIV

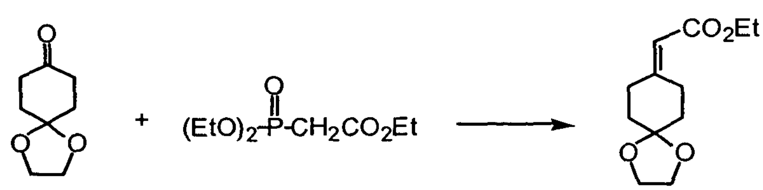
The desired product **XXXIV** was prepared according to the procedure in Example XXIX, Steps 4-5.

Example XXXV: Preparation of a compound of formula XXXV:



XXXV

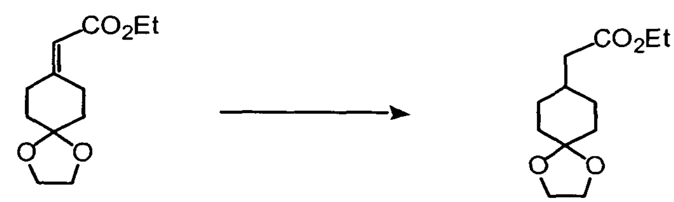
Step 1:



A solution of triethyl phosphonate (44.8 g) in THF (30 mL) at 0°C was treated with a 1M solution (200 mL) of sodium bis(trimethylsilylamide) in THF. The resulting mixture was stirred at RT for 0.5 hour, and then cooled to 0°C. A solution of 1,4-cyclohexanedione ethylene ketal (15.6 g) in THF (50 mL) was

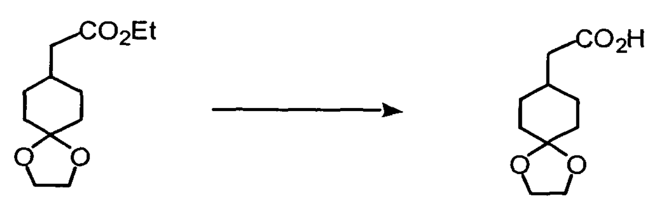
added dropwise, and the resulting solution was stirred at RT for 18 hours. The reaction mixture was then cooled to 0°C, treated with cold aqueous citric acid, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/EtOAc to afford the title compound (21 g), 92% yield. Mass spectrum (FAB) 227.3 ($M+H^+$).

Step 2:



The product of the preceding step (20 g) was dissolved in EtOH (150 mL) and treated with 10% Pd/C under 1 atm of hydrogen for 3 days. The mixture was filtered and the filtrate evaporated to afford the title compound (20.3 g), 100 % yield. Mass spectrum (FAB) 229.2 ($M+H^+$).

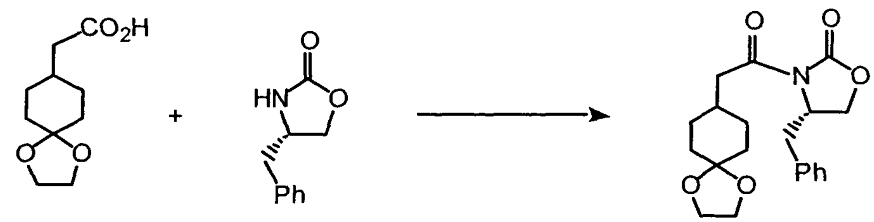
Step 3:



The product of the preceding step (20 g) was dissolved in MeOH (150 mL) and treated with a solution of LiOH (3.6 g) in water (50 mL). The mixture was stirred for 18 hours, and concentrated under vacuum. The residue was dissolved in cold water (100 mL), the solution was acidified to pH 2-3 with 5N HCl, and the resulting mixture was extracted with EtOAc. The extract was dried over

anhydrous Na_2SO_4, filtered, and the filtrate evaporated to afford the title compound (17.1 g), 97% yield. Mass spectrum (FAB) 201.2 ($M+H^+$).

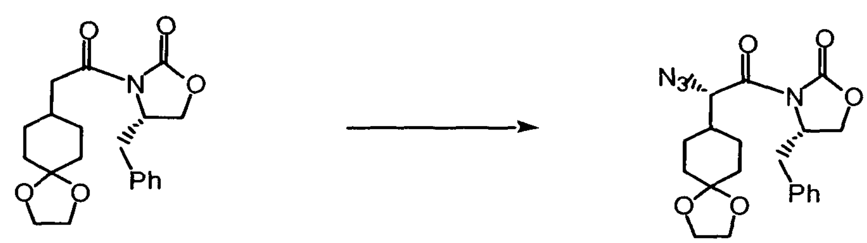
Step 4:



1. The product of the preceding step (3.0 g) was dissolved in Et_2O (150 mL), treated with Et_3N (2.1 mL), and the solution cooled to -78°C. Pivaloyl chloride (1.85 mL) was added dropwise, and after 0.25 hour additional stirring, the reaction was allowed to warm to 0°C over 0.75 hour, and then cooled again to -78°C to afford a solution of mixed anhydride for reaction in part 2.

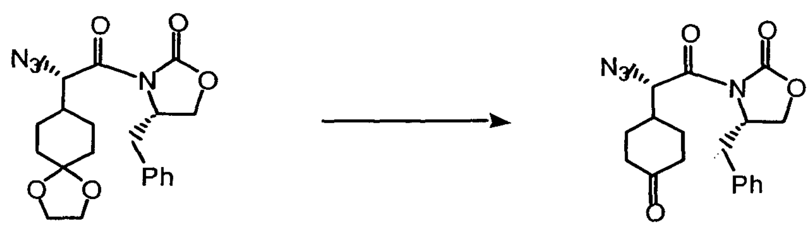
2. A solution of (S)-4-benzyl-2-oxazolidinone (2.66 g) in THF (22 mL) was cooled to -78°C, and a 1.6 M solution (9.38 mL) of n-butyllithium in hexane was added dropwise. After an additional 0.33 hour stirring at this temperature, the solution was transferred via canula to the cold solution of part 1. The mixture was stirred at -78°C , then warmed to 0°C, and stirred at this temperature for 0.5 hour. The organic layer was separated, the aqueous layer was extracted with Et_2O, the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of hexane/EtOAc (9:1) to afford the title compound (5.0 g), 93% yield. Mass spectrum (FAB) 360.4 ($M+H^+$).

Step 5:



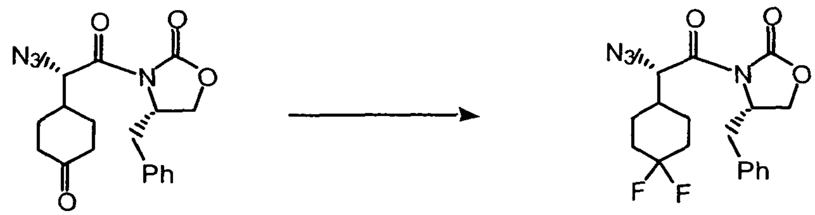
The product of the preceding step (2.7 g) was dissolved in THF (25 mL), cooled to -78°C, transferred by canula to a solution of 0.5 M potassium bis(trimethylsilyl)amide/toluene (16.5 mL) in THF (25 mL) at -78°C, and the resulting solution was stirred at -78°C for 0.75 hour. To this solution was added via canula a solution of trisyl azide (3.01 g) in THF (25 mL) pre-cooled to -78°C. After 1.5 minutes, the reaction was quenched with acetic acid (1.99 mL), the reaction was warmed to RT, and then stirred for 16 hours. The reaction was diluted with EtOAc (300 mL), and washed with 5% aqueous NaCl. The aqueous phase was extracted with EtOAc, the combined organic phases were washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane (1:3) to afford the title compound (2.65 g), 88% yield.

Step 6:



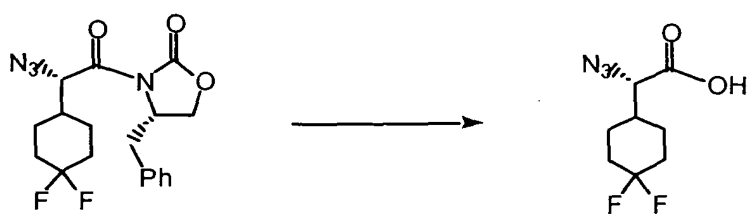
The product of the preceding step (11.4 g) was dissolved in 95% formic acid (70 mL) and heated at 70°C for 0.5 hour while stirring. The solution was evaporated under vacuum, and the residue was taken up in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel to afford the title compound (8.2 g).

Step 7:



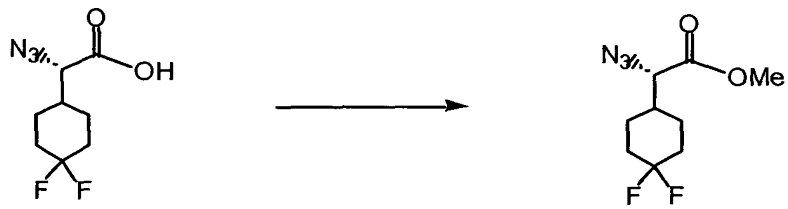
The product of the preceding step (8.2 g) was dissolved in CH_2Cl_2 (16 mL) and treated with diethylaminosulfur trifluoride (DAST, 7.00 mL) at RT for 3 hours. The reaction was poured over ice/water (200 cc), and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane (15:85) to afford the title compound (4.5 g), 52% yield.

Step 8:



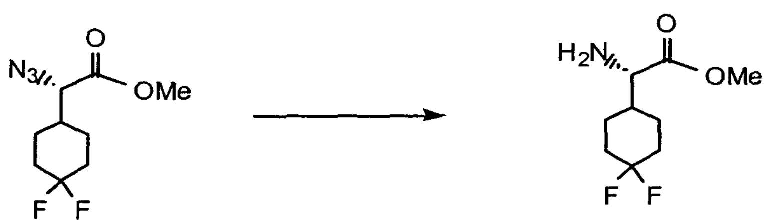
The product of the preceding step (3.7 g) was dissolved in a mixture of THF (150 mL) and water (48 mL), cooled to 0°C, treated with 30% H_2O_2 (3.95 mL), and then with $LiOH{\cdot}H_2O$ (0.86 g). The mixture was stirred for 1 hour at 0°C, then quenched with a solution of Na_2SO_3 (5.6 g) in water (30 mL), followed by a solution of 0.5 N $NaHCO_3$ (100 mL). The mixture was concentrated under vacuum to 1/2 volume, diluted with water (to 500 mL), and extracted with CH_2Cl_2 (4 x 200 mL). The aqueous phase was acidified to pH 1-2 with 5N HCl, and extracted with EtOAc (4 x 200 mL). The extract was washed brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated to afford the title compound (1.95 g), 91% yield, which was used directly in the next step.

Step 9:



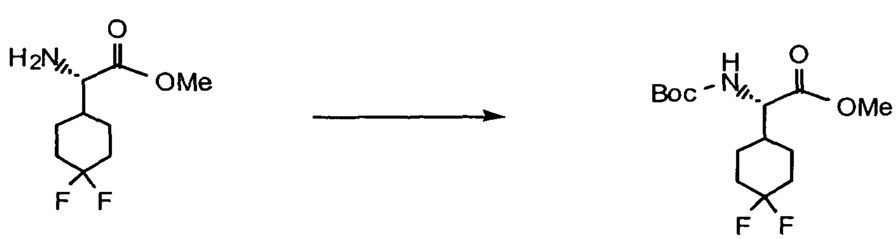
The product of the preceding example (2.6 g) was dissolved in Et_2O (50 mL) and treated dropwise with a solution of CH2N2 in Et_2O until the solution remained yellow. The solution was stirred for 18 hours, then evaporated under vacuum to afford the title compound (2.8), which was used directly in the next step.

Step 10:



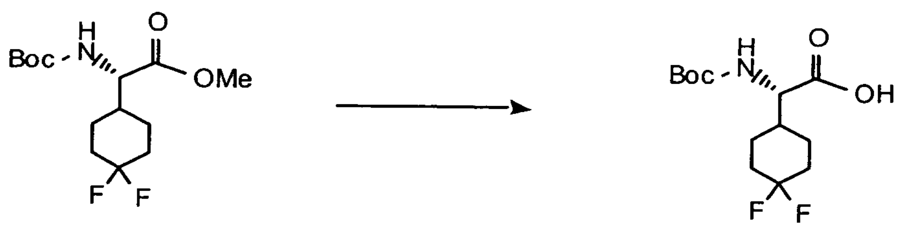
The product of the preceding step (1.95 g) was dissolved in MeOH (150 mL), treated with formic acid (1.7 mL), then treated with 10% Pd/C (3.3 g, Degussa type E101) under 1 atm of hydrogen for 1.5 hours. The mixture was filtered and the filtrate evaporated to afford the title compound (2.1 g) as the formic acid salt, which was used directly in the next step.

Step 11:



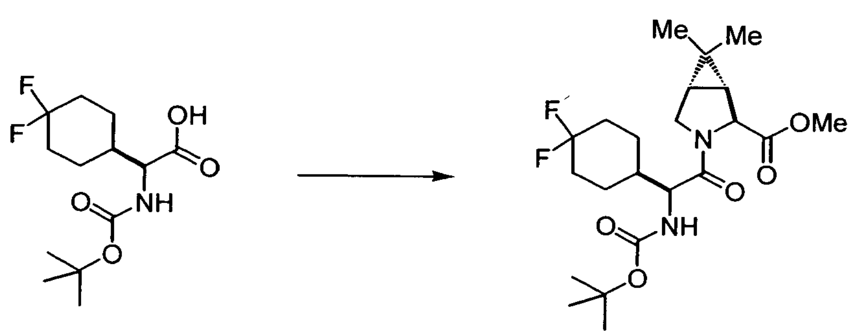
The product of the preceding step (2.1 g) was dissolved in 1,4-dioxane (100 mL) and di-*tert*-butyl dicarbonate (1.9 g) was added, followed by diisopropylethylamine (2.9 mL). The solution was stirred for 18 hours, and concentrated under vacuum. The residue was treated with aqueous 5% KH_2PO_4 and the mixture extracted with EtOAc. The extract was washed with brine; then dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/Et_2O to afford the title compound (2.5 g), 99% yield. Mass spectrum (FAB) 307.9 ($M+H^+$).

Step 12:



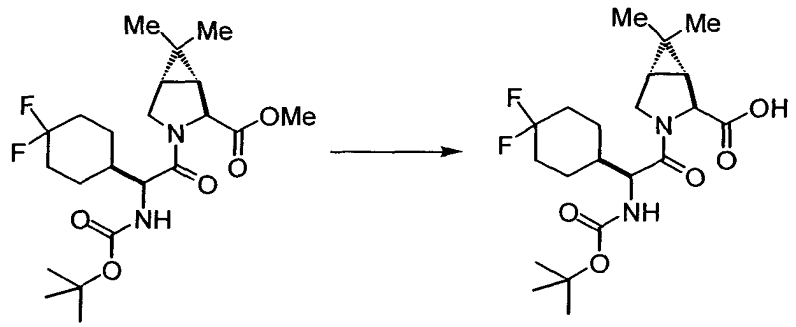
The product of the preceding step (2.5 g) was dissolved in 1,4-dioxane (35 mL), treated with aqueous 1M LiOH (17 mL), and stirred for 2 hours. The mixture was quenched with ice/water (125 cc), the mixture was acidified to pH 3-4 with 3N HCl, and extracted with EtOAc. The extract was dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated to afford the title compound (2.3 g), 96% yield. Mass spectrum (FAB) 294.0 ($M+H^+$).

Step 13:



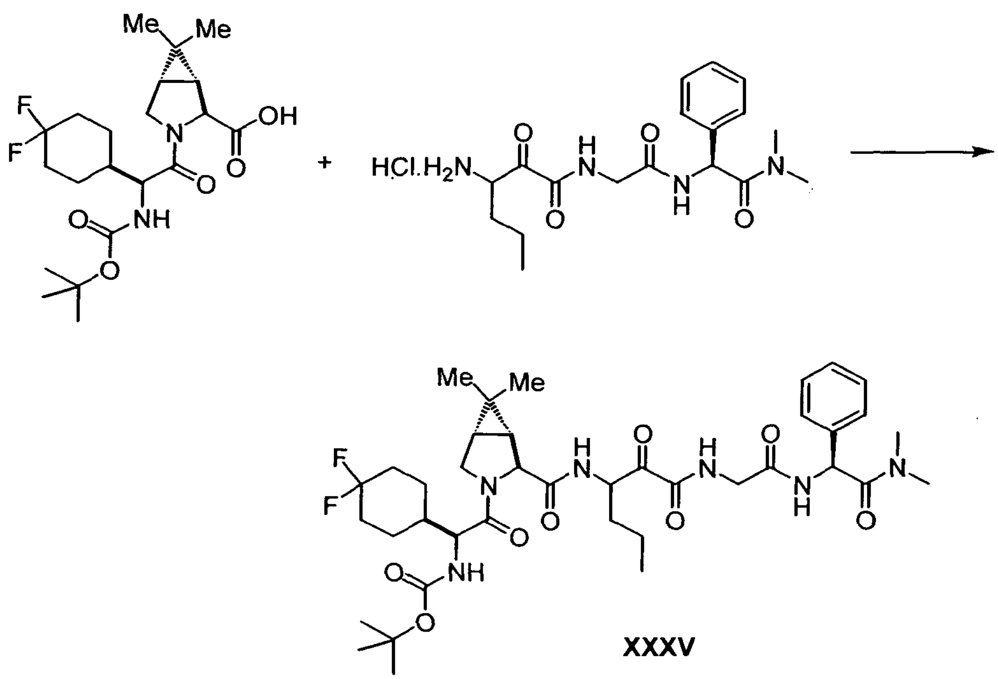
The desired product was prepared according to the procedure in Example XXIII, Step 10.

Step 14:



The desired acid product was prepared according to the procedure in Example XXIV, Step 3.

Step 15:

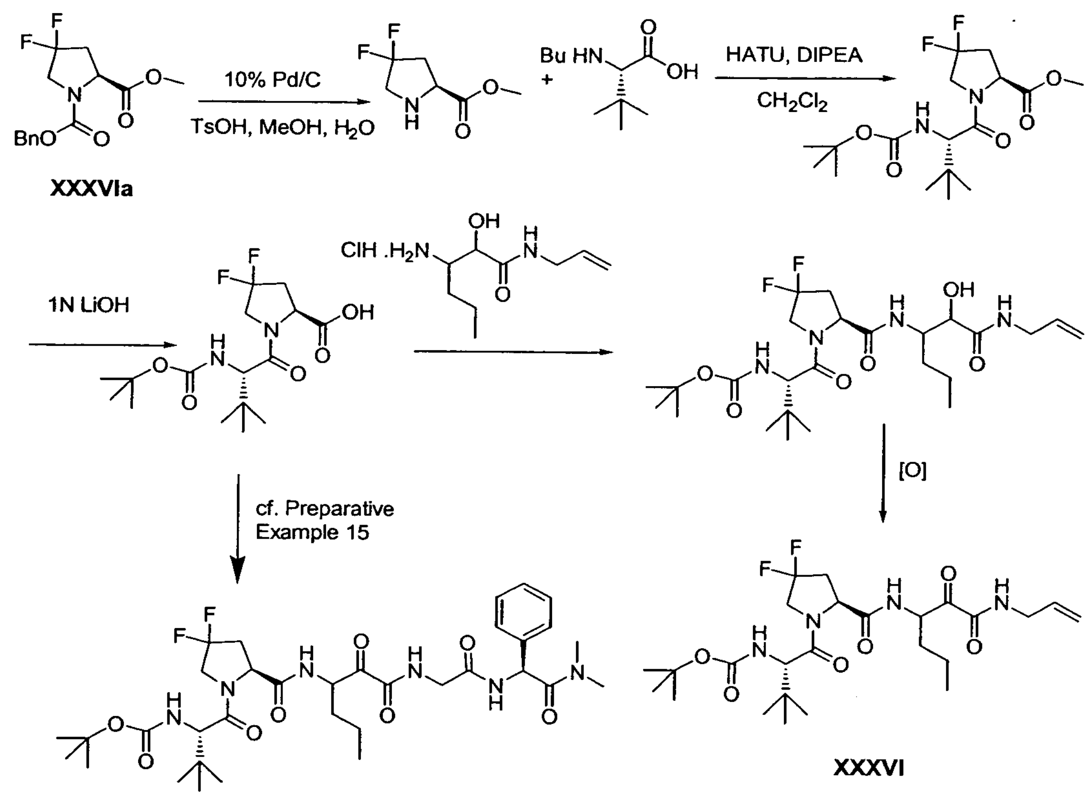


XXXV

The desired acid product was prepared according to the procedure in Example XXIX, Step 4.

Example XXXVI. Preparation of compounds of Formulas XXXVI and XXXVIII:

Compounds of formulas XXXVI and XXXVIII were prepared according to the scheme below and utilizing preparative Examples 11 through 15 discussed above.

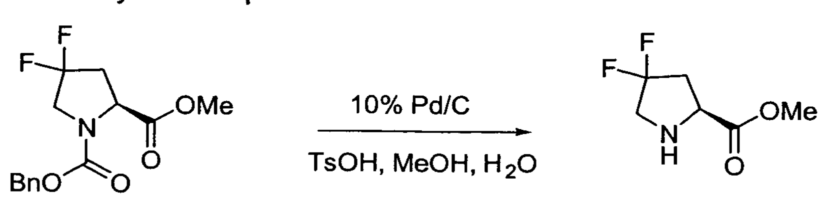


XXXVIa

XXXVI

XXXVII

The compound of formula XXXVIb was prepared from a compound of formula XXXVIa as follows by known procedures:



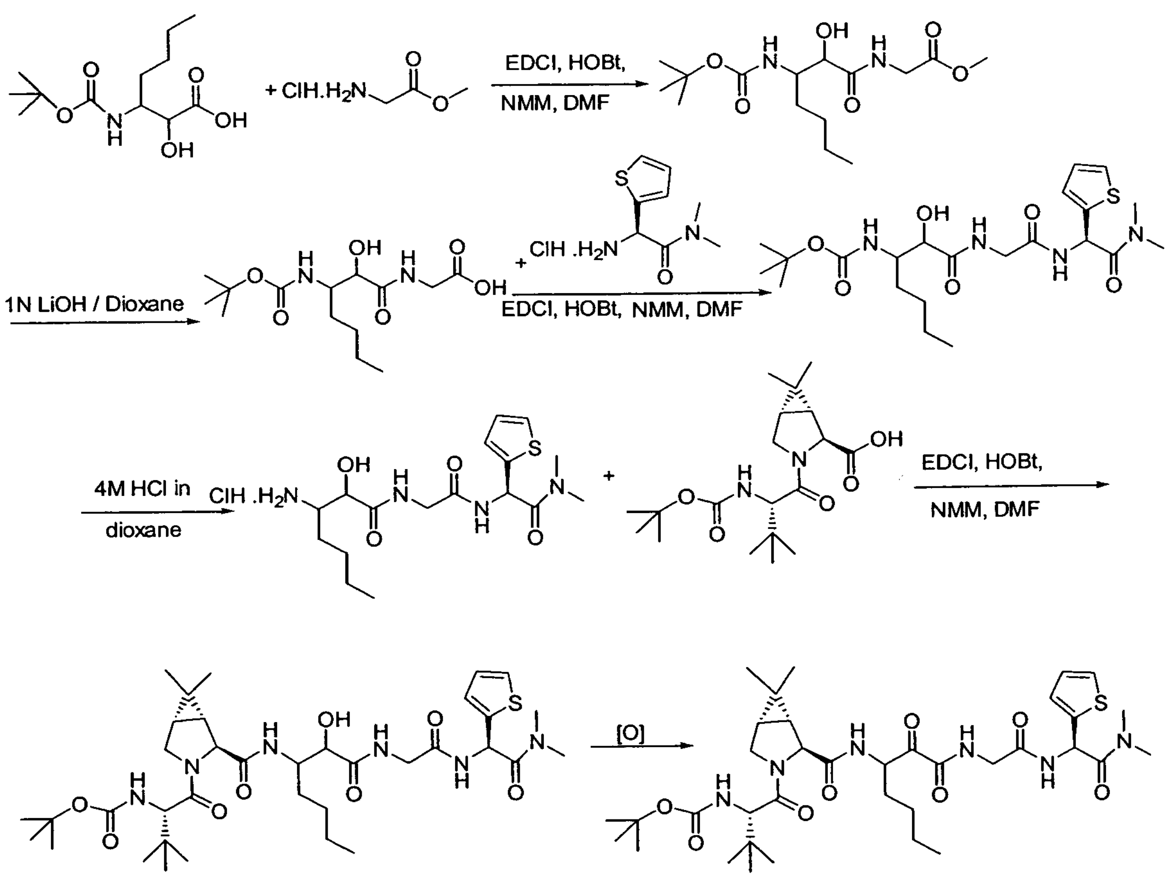
XXXVIa

XXXVIb

To a solution of Compound XXXVIa (6.58g, 22 mmol) in 100 mL of MeOH was added 10% Pd/C (0.8 g) and *p*-toluene sulfonic acid (4.2 g). The reaction mixture was subjected to hydrogenation at room temperature overnight. The reaction mixture was filtered through celite and washed with excess MeOH. The combined filtrate was concentrated in-vacuo to provide the title compound XXXVIb as a gummy. Conversion of XXXVIb to XXXVI and XXXVII followed the route as shown in the scheme above and according to preparative examples 11-15.

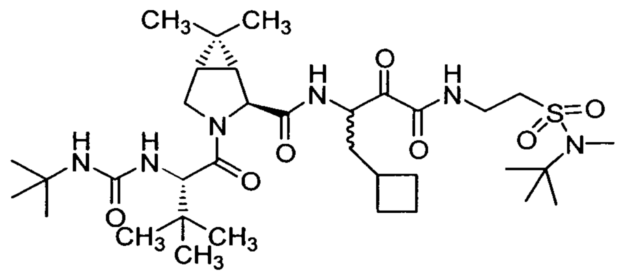
Example XXXVIII. Preparation of a compound of formula XXXVIII:

A compound of the formula XXXVIII was prepared utilizing the following scheme and following preparative Examples 11 through 15 discussed earlier.



XXXVIII

Example XXXIX. Synthesis of the compound of Formula XXXIX:



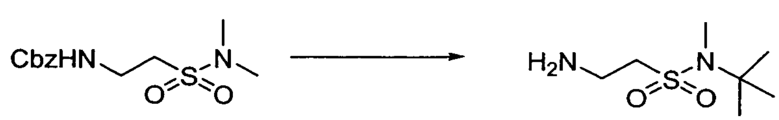
XXXIX

Step 1:

XXXIXa **XXXIXb**

A solution of the sulfonyl chloride XXXIXa prepared by the procedure of H. Mcklwain *(J. Chem. Soc* 1941, 75) was added dropwise to a mixture of 1.1. equiv of t-butylmethylamine and triethylamine at –78 °C and stirred at rt for 2h. The reaction mixture was concentrated in vacuo and purified by chromatography (SiO_2, Hex/Acetone 4:1) to yield sulfonamide XXXIXb as a colorless oil.

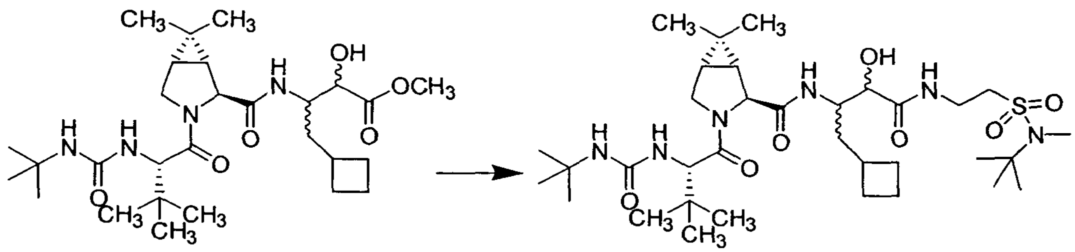
Step 2:



XXXIXb **XXXIXc**

A solution of the Cbz-protected amine XXXIXb was dissolved in methanol and treated with 5 mol% of Pd /C (5%w/w) and hydrogenated at 60 psi. The reaction mixture was filtered through a plug of celite and concentrated in vacuo to obtain the free amine XXXIXc which solidfied on standing.

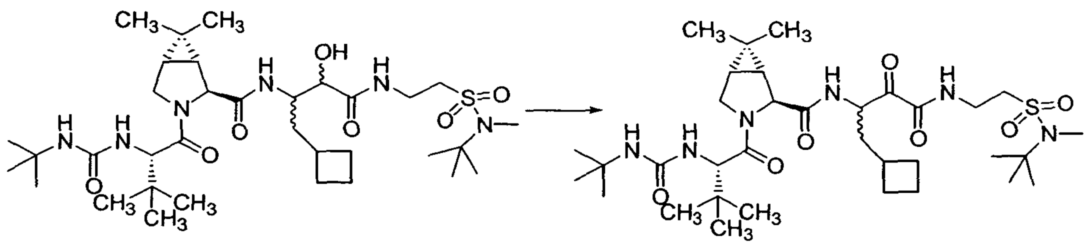
Step 3:



XXVe XXXIXd

The hydroxy sulfonamide XXXIXd was synthesized similar to the procedure for the synthesis of XXVf except replacing the amine XXVd with XXXIXc. The crude reaction mixture directly used for the next reaction.

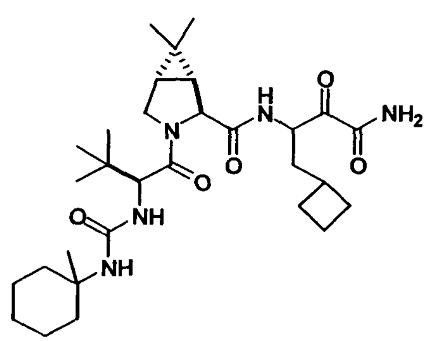
Step 4:



XXXIXd XXXIX

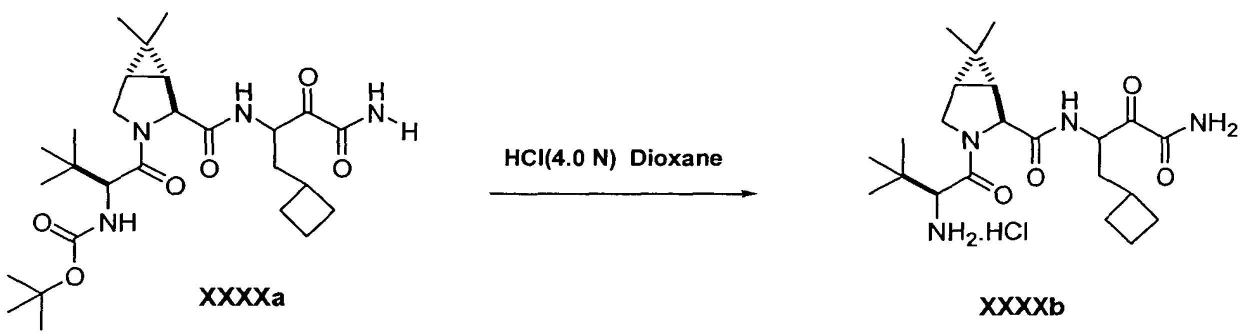
The hydroxy amide XXXIXd was oxidized to compound XXXIX using the Dess Martin reagent following the procedure for the synthesis of XXV (step 5). The crude mixture was purified by chromatography (SiO_2, Acetone/Hexane 3:7) to obtain XXXIX as a colorless solid.

Example XXXX Preparation of Compound of Formula XXXX



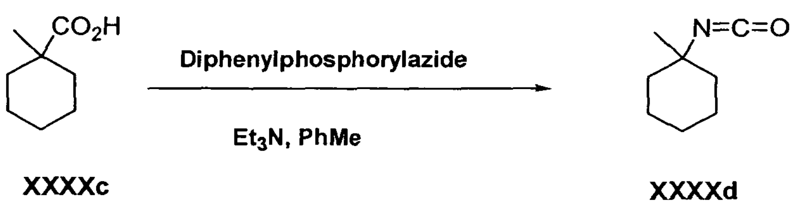
XXXX

Step1



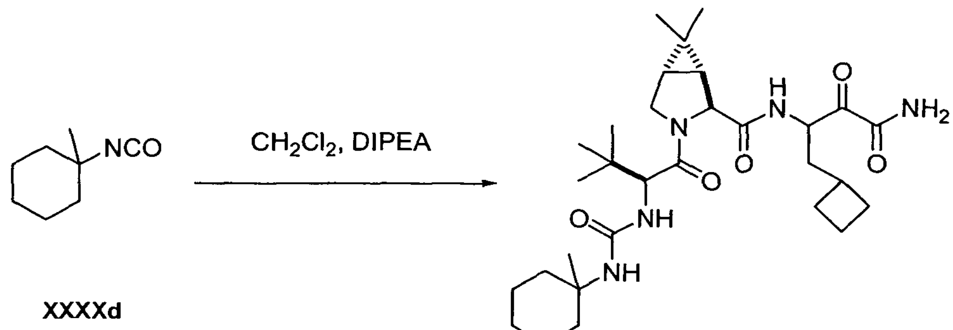
XXXXa was reacted in the manner previously described XXXII step 1 to afford XXXXb product product of step 1 Mass spectrum (LCMS) 421 (M – HCl +H+).

Step2



Et_3N(1.4 mL) and Diphenylphosphorylazide(2.2 mL) were added to a solution of carboxylic acid **XXXXc** in toluene (13 mL). Reaction was stirred at RT for 30 min then refluxed overnight. After 18 h, reaction is cooled to RT and **XXXXd** product of step2, which was used directly 0as a 0.7 M solution in Toluene.

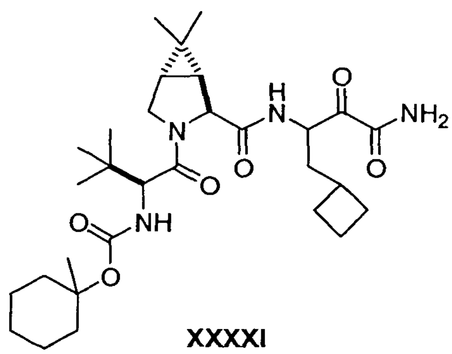
Step 3



XXXXd **XXXX**

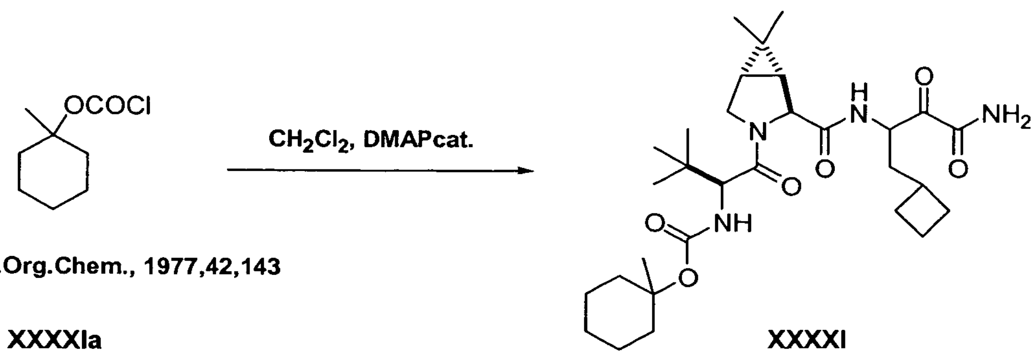
XXXXb, Product of step 1 of preparative example **XXXX** was reacted with **XXXXd** product of step 2 of preparative example **XXXX** in the manner previously described in example XXXIII to afford **XXXX**. Mass spectrum (LCMS) 560 ($M+H^+$).

Example XXXXI Preparation of Compound of Formula XXXXI



XXXXI

Step4

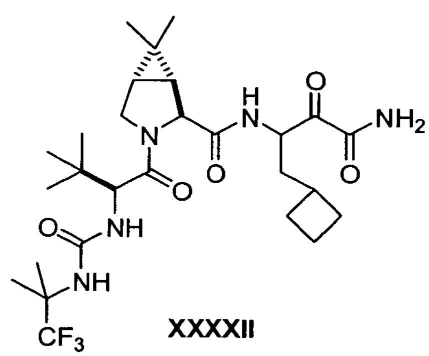


Prepared cf J.Org.Chem., 1977,42,143

XXXXIa **XXXXI**

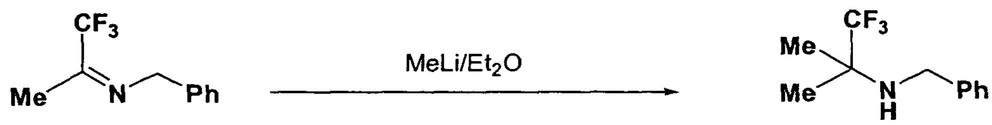
XXXXb, product of step 1 of preparative example **XXXX** was reacted with chloroformate **XXXXIa** prepared as ***J.Org.Chem.***,1977,42,143 in the manner previously preparative example 12 compound 4.1 described to afford **XXXXI**. Mass spectrum (LCMS) 561 (M+H$^+$).

Example XXXXII Preparation of Compound of Formula XXXXII



XXXXII

Step1



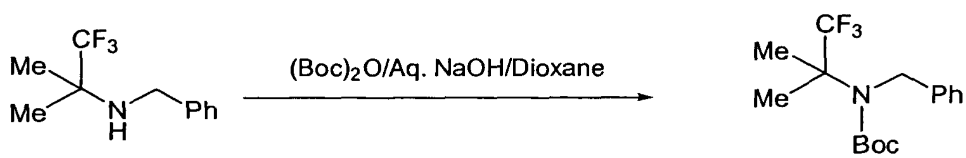
Prepared cf J.Org.Chem., 1996 p 6567

XXXXIIb

XXXXIIa

To a stirred and cooled (acetone/dry ice bath) solution of the starting imine **XXXXII a** (3.679 g) in diethyl ether (50 ml) was added 1.6M methyl lithium in diethyl ether (12.6 ml). The reaction mixture was allowed to warm up to room temperature over 2 hrs. Saturated $NaHCO_3$ was added and after stirring for ~30 min the organic phase was separated. It was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The crude product was subjected to chromatography over silica gel (2% ethyl acetate in n-hexane) to provide the desired product **XXXXIIb** (0.3 g).

Step 2

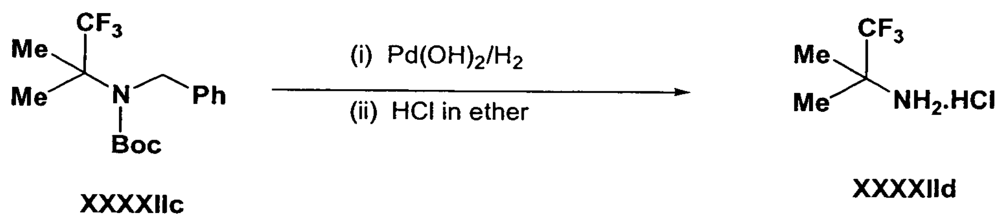


XXXXIIb

XXXXIIc

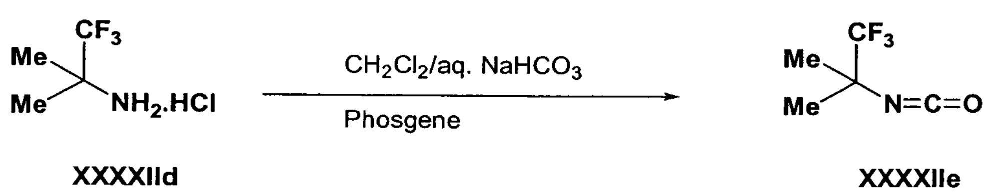
To a stirred and cooled (ice bath) solution of **XXXXIIb** the product from step 1 (0.3 g) was added 1.0N NaOH (1.38 ml) followed by $(Boc)_2O$. The reaction mixture was stirred at room temperature for ~20 hrs after which it was distributed between ethyl acetate (50 ml) and water (10 ml). The ethyl acetate phase was separated, washed with brine and dried over anhydrous Na_2SO_4. Evaporation under vacuum to dryness provided the desired NBoc derivative **XXXXIIc** (0.660 g), which was used without further purification in the following step.

Step 3



A solution of the **XXXXIIc** product from step 2 in methanol (10 ml) was hydrogenated in the presence of $Pd(OH)_2$ until thin layer chromatography showed the absence of the starting material. $Pd(OH)_2$ was removed by filtration and washed with methanol. The combined filtrate and washings were concentrated to dryness under vacuum to provide a solid which was dissolved in methanol and treated with 1.0N HCl in diethyl ether. After ~2 hr the reaction mixture was evaporated to dryness under vacuum to provide **XXXXIId** the desired amine hydrochloride as a white solid (0.2 g).

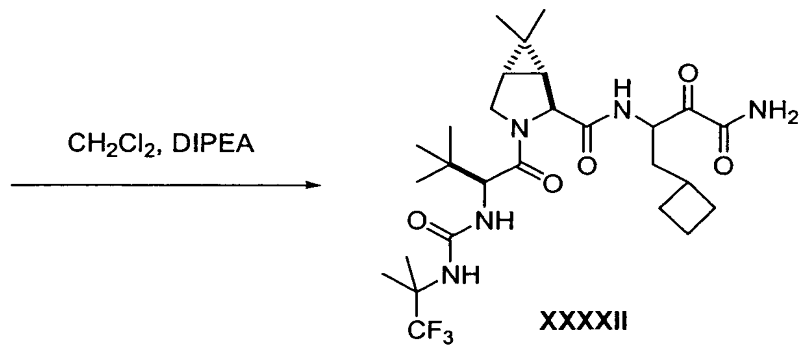
Step 4



To a stirred and cooled (ice bath) solution of **XXXXIId** the product from step C (0.1 g) in CH_2Cl_2 (6 ml) was added saturated $NaHCO_3$ solution (4 ml) followed by phosgene (0.64 ml). The reaction mixture was stirred at 0°C for 30 min and at room temperature for 1 hr. The organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated to dryness in vacuum to provide the desired isocyanate **XXXXIIe** (0.0611 g).

Step 5

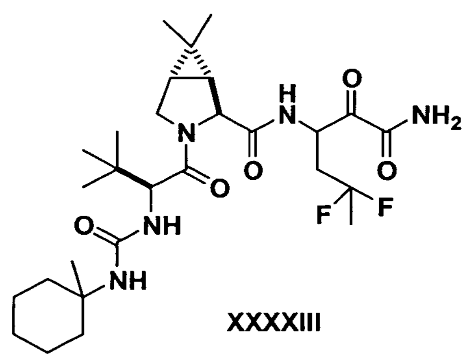
XXXXb



XXXXII

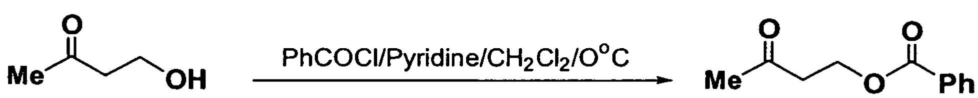
XXXXIIe, product of step 5 was reacted with **XXXXb** of preparative example **XXXX** in the manner previously **in example XXXIII** described to afford **XXXXII**. Mass spectrum (LCMS) 574 ($M+H^+$).

Example XXXXIII Preparation of Compound of Formula XXXXIII



XXXXIII

Step 1

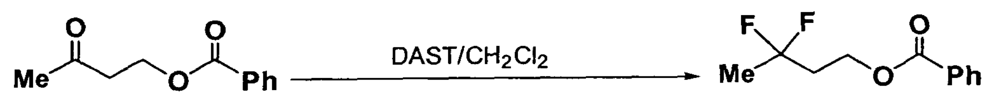


XXXXIIIa XXXXIIIb

To a cooled solution (ice bath) of 4-hydroxy-2-butanone (8.81 g) **XXXXIIIa** in CH_2Cl_2 (100 ml) was added with stirring, benzoyl chloride (14.76 g) followed by pyridine (16.15 ml) and DMAP (0.01 g). The reaction mixture was stirred at room temperature overnight then diluted with ethyl acetate (~200 ml). The solution was

washed with aqueous $CuSO_4$, aqueous NH_4Cl and brine. The organic phase was then dried over anhydrous $MgSO_4$ and evaporated to dryness. The product was purified by column chromatography over silica gel (5%-15% ethyl acetate in n-hexane) to provide **XXXXIIIb** (16.3 g; 84.9%).

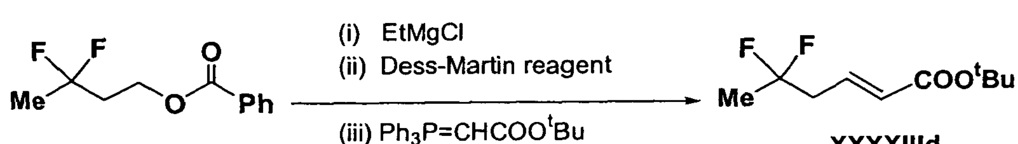
Step 2



XXXXIIIb **XXXXIIIc**

To a solution of **XXXXIIIb**, the product from step 1 (16.3 g) in CH_2Cl_2 (150 ml), was added DAST (26.1 ml) and the reaction mixture stirred at room temperature for ~72 hrs. The mixture was then added dropwise to a cold saturated solution of Na_2CO_3 (150 ml). The mixture was diluted with ethyl acetate (~200 ml) and after stirring for ~30 min the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuo and purification by chromatography over silica gel (4% ethyl acetate in n-hexane) provided **XXXXIIIc** (14.6 g; 80.4%).

Step3



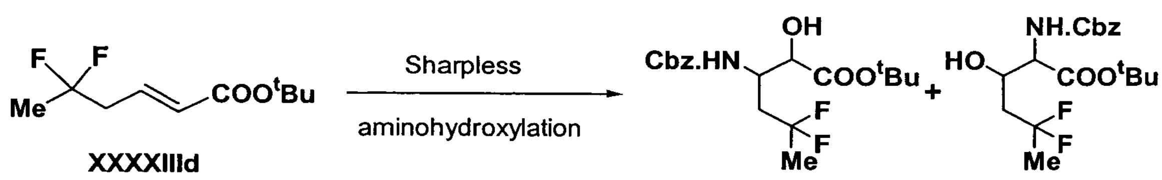
XXXXIIIc **XXXXIIId**

To a solution of **XXXXIIIc** the product from step 2 (4 g) in dry diethyl ether (150 ml) was added with cooling (ice bath) EtMgCl (28 ml). The reaction mixture was stirred in the cooling bath for ~6 hrs after which it was poured into saturated aqueous NH_4Cl with ice cooling. The organic layer was separated, washed with

brine, dried over anhydrous $MgSO_4$ and concentrated to dryness in vacuum. The residue was dissolved in CH_2Cl_2 (100 ml) and treated with Dess-Martin reagent (15.8 g). After stirring at room temperature for 1 hr $Ph_3P{=}CHCOO^tBu$ (10.54 g) was added. Stirring was continued for ~20 hrs. Ethyl acetate (~200 ml) was added followed by a mixture of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ (200 ml; 1/1) and stirred for ~ 10 min. The organic layer was separated and washed successively with saturated NaHCO3 and brine. The washed organic phase was dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum to provide the desired crude product.

The above reaction was repeated using the product from step 2 (10.6 g). The final crude products from the two reactions were combined and subjected to purification by chromatography on silica gel (10% CH_2Cl_2 in n-hexane) to provide **XXXXIIId** (7.93 g; 57%).

Step 4



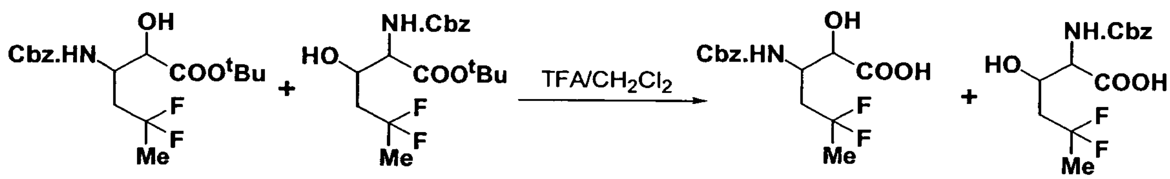
XXXXIIId XXXXIIIe XXXXIIIf

Benzyl carbamate (8.92 g) was dissolved in n-propyl alcohol (79 ml). To the resulting solution was added with stirring a freshly prepared solution of NaOH (2.33 g) in water (145 ml), followed by tert-butylhypochlorite (6.57 ml). To the resulting mixture $(DHQ)_2PHAL$ (0.742 g) dissolved in n-propyl alcohol (66 ml) was added followed by **XXXXIIId** (19.05 mmol). The osmium catalyst, $K_2OsO_2(OH)_2$ was then added and the reaction mixture stirred at room temperature for 1 hr.

The above reaction was repeated using **XXXXIIId** (19. 36 mmol). The two reactions were combined followed by dilution with ethyl acetate (500 ml). The mixture was shaken with water (100 ml), the organic phase separated and

washed with water, brine and finally dried over anhydrous $MgSO_4$. Evaporation under vacuum provided the crude product which was chromatographed over silica gel (10%-20% ethyl acetate in n-hexane) to provide pure desired product (3 g) as a mixture of **XXXXIIIe** and **XXXXIIIf**

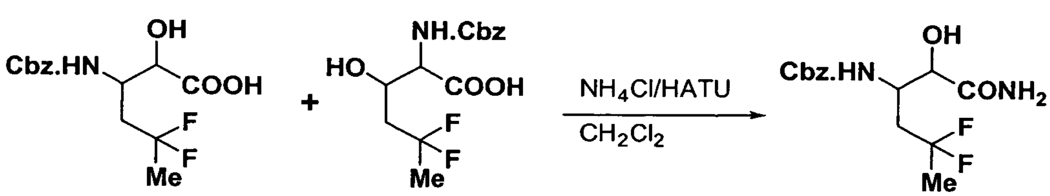
Step 5



XXXXIIIe XXXXIIIf XXXXIIIg XXXXIIIh

A stirred solution of **XXXXIIIf** and **XXXXIIIe** the product from step 4 in CH_2Cl_2 (50 ml) was treated with trifluoroacetic acid (50 ml). After 4 hrs the reaction mixture was concentrated to dryness under vacuum. The residue was dissolved in 10% aqueous Na_2CO_3 the solution washed with diethyl ether and the aqueous phase acidified with 2M H_2SO_4 to pH ~1.5. Extraction of the acidic solution with ethyl acetate followed by drying over anhydrous MgSO4 and evaporation under vacuum provided the desired product as a mixture of **XXXXIIIg** and **XXXXIIIh** (2.6 g).

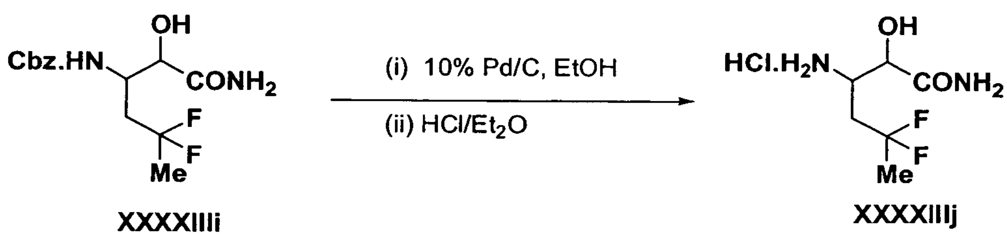
Step 6



XXXXIIIg XXXXIIIh XXXXIIIi

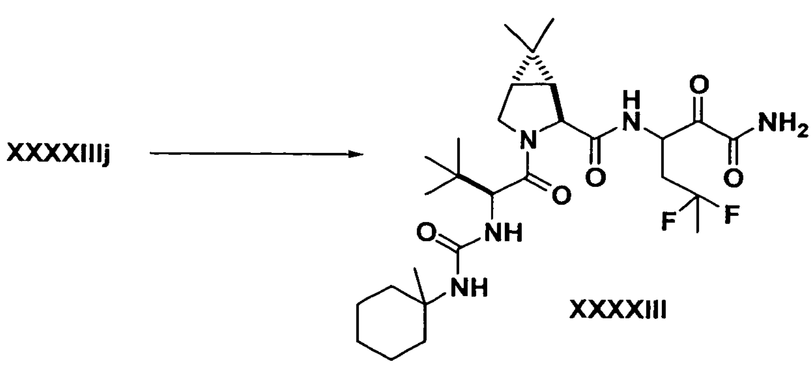
To a solution of the product from step 5 (1 g) in CH_2Cl_2 (50 ml) was added HATU (1.43 g), NH_4Cl (0.842 g) and DMSO (5.59 ml). The reaction mixture was stirred at room temperature for ~20 hrs, diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$ and concentrated to dryness under vacuum to provide the crude product. Chromatography on silica gel (10% n-hexane in ethyl acetate) provided in one of the fractions the pure desired product **XXXXIIIi** (0.205 g).

Step 7



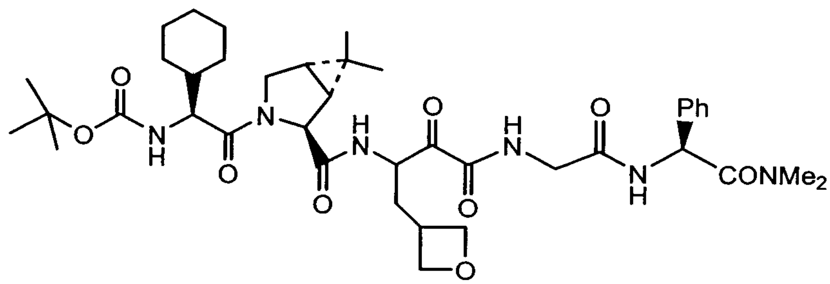
To a solution of **XXXXIIIi** the product from step 6 (0.205 g) in ethanol (15 ml) was added 10% Pd/C catalyst. The resulting suspension was hydrogenated until thin layer chromatography indicated complete consumption of the starting material (~3 hrs). The catalyst was removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product **XXXXIIIj** (0.164 g).

Step 8



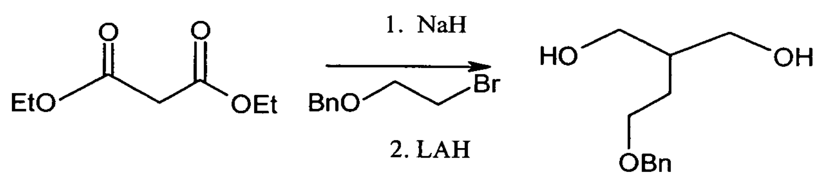
XXXXIIIj was converted to **XXXIII** following the procedure similar to exmple **XXVIII** and **XXXIII**

Example XXXXIV Preparation of Compound of Formula XXXXIV



XXXXIV

Step 1

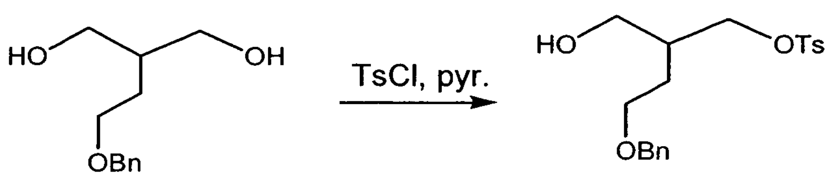


XXXXIVa **XXXXIVb**

Ethyl malonate **XXXXIVa** (5.4ml; 36mmol) was added to a suspension of NaH (1.44g of a 60% dispersion in mineral oil; 0.9eq.) in anhydrous tetrahydrofuran (THF; 60ml) at 0C, under an atmosphere of nitrogen and the mixture was stirred at room temperature for 30 min. Benzyl 2-bromoethylether (8.5ml; 40mmol) was added before refluxing the reaction for a period of 24h. After cooling, the reaction was partitioned between EtOAc and dilute HCl (approx. 1M). The organic layer was separated, dried ($MgSO_4$) and concentrated to yield a residue.

The aforementioned residue was dissolved in anhydrous THF (100ml) and a solution of lithium aluminum hydride (LAH; 66ml of a 1.0M solution) was added under an atmosphere of nitrogen and the resulting mixture was stirred at room temp. for a period of 4h. and EtOAc followed by dilute HCl was added. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction product was purified by silica gel column chromatography using EtOAc:Hexane (70:30) as eluent to provide the desired diol **XXXXIVb** (3.59g) as a colourless oil.

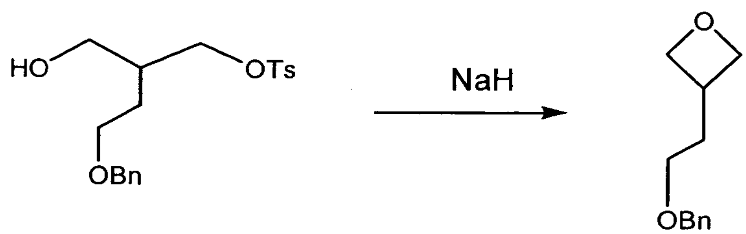
Step 2



XXXXIVb **XXXXIVc**

p-Toluene sulfonylchloride (1.12g; 5.9mmol) was added to the diol **XXXXIVb** (1.00g; 4.9mmol) in a mixture of dichloromethane (15ml) and pyridine (1.18ml; 14.6mmol) and the resulting mixture was stirred at room temperature overnight (approx 16h.). The reaction mixture was partitioned between EtOAc and dilute aqueous HCl. The organic phase was separated, washed with sat. aq. Sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced preesure. The residue was purified by silica gel column chromatography using EtOAc: hexane (30:70) as eluent to provide I) the ditosylate (0.291g), followed by ii) the desired mono-tosylate **XXXXIVc** (1.02g) and iii) recovered diol (0.27g).

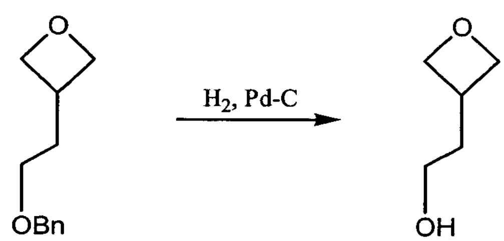
Step 3



XXXXIVc **XXXXIVd**

The mono-tosylate **XXXXIVc** (1.0g; 2.8mmol) in anhydrous dimethylformamide (DMF; 3ml) was added to a suspension of NaH (0.333g of a 60 % dispersion in mineral oil; 8.3mmol) in DMF (13ml) and the resulting mixture was stirred at room temperature for a period of 3h. The reaction mixture was partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried (MgSO4) and concentrated to provide a residue which was purified by silica gel column chromatography using EtOAc: hexane (1:5) as eluent to provide the desired oxetane **XXXXIVd** (0.37g) as a colourless oil.

Step 4



XXXXIVd **XXXXIVe**

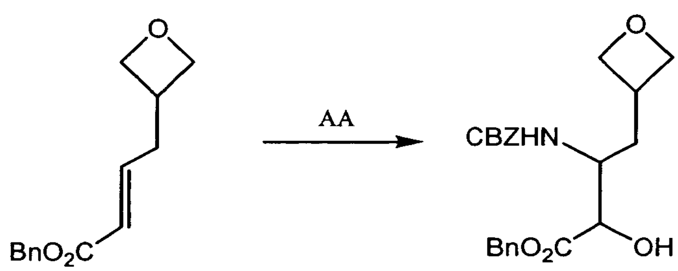
A suspension of 10% Pd-C (0.10g) and the benzylether **XXXXIVd** (0.33g) in methanol (10ml) was placed under an atmosphere of hydrogen (balloon) for a period of 1h. The reaction mixture was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure to provide the alcohol **XXXXIVe** (0.17g) as a colourless oil used in subsequent procedures without purification.

Step 5

XXXXIVe **XXXXIVf**

The Dess-Martin periodinane (0.658g; 0.16mmol) was added to a solution of the alcohol **XXXXIVe** (0.144g; 1.4mmol) in dichloromethane (5ml) and stirred at room temperature for a period of 1h., before adding the phosphorane (0.637g; 0.16mmol). The resulting reaction mixture was stirred for a period of approx. 16h., then partitioned between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexane; 1:5 to provide the ester **XXXXIVf** (0.131g) as a colourless oil.

Step 6

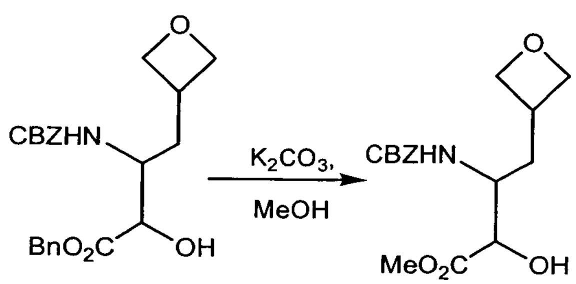


XXXXIVf **XXXXIVg**

Benzyl carbamate (0.657g; 4.3mmol) was dissolved in n-propanol (6ml). Aqueous sodium hydroxide (0.171g; 4.3mmol, in 11ml of water) was added followed by tert-butyl hypochlorite (0.49ml; approx 4.3mmol) and a solution of $(DHQ)_2PHAL$ (0.056g) in n-propanol (5ml). The resulting mixture was placed in a

water bath and and stirred for 5 min. before adding the olefin **XXXXIVf** (0.326g; 1.4mmol) followed by potassium osmate dihydrate (0.021g). The resulting reaction mixture was sirred for 3h., and added to EtOAc. The aqueous layer was separated and washed with EtOAc. The combined organic phases were wahed with brine, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc; hexane (7:3) as eluent to give the alpha-hydroxy ester **XXXXIVg** (0.367g), containing approx. 20% of the undesired beta-hydroxy ester.

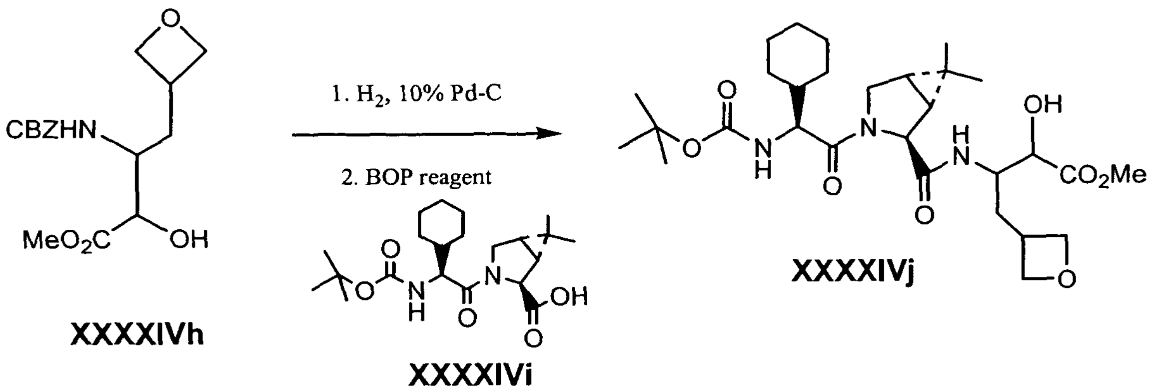
Step 7



XXXXIVg **XXXXIVh**

Potassium carbonate (0.100g) was added to a methanol (30ml) solution of approx. 2g of the benzyl ester **XXXXIVg** (contaminated with a small quantity of benzyl carbamate). The resulting mixture was stirred at room temperature for 2h., then partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (7:3) to provide the ester **XXXXIVh** (1.02g).

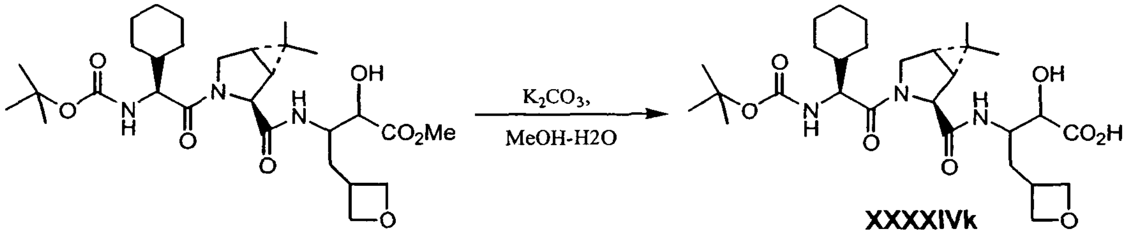
Step 8



A suspension of 10% Pd-C (0.030g) and the benzyl carbamate **XXXXIVh** (0.090g) in methanol (5ml) was placed under an atmosphere of hydrogen (balloon) for a period of 1h. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure to yield the intermediate amine (0.050g) which was used immediately.

BOP reagent (0.131g; 0.31mmol) followed by triethylamine (0.130ml;0.93mmol) were added to amixture of the amine (0.050g; 0.28mmol) and the carboxylic acid **XXXXIVi** (0.121g; 0.31mmol) in dichloromethane (3ml) and the resulting mixture was stirred for a period of 4h. and partitioned between dil. aq. HCl (approx. 1M) and EtOAc. The organic phase was separated, washed with sat. aq. Sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc as eluent to provide the methyl ester **XXXXIVj** (0.107g) as a white solid.

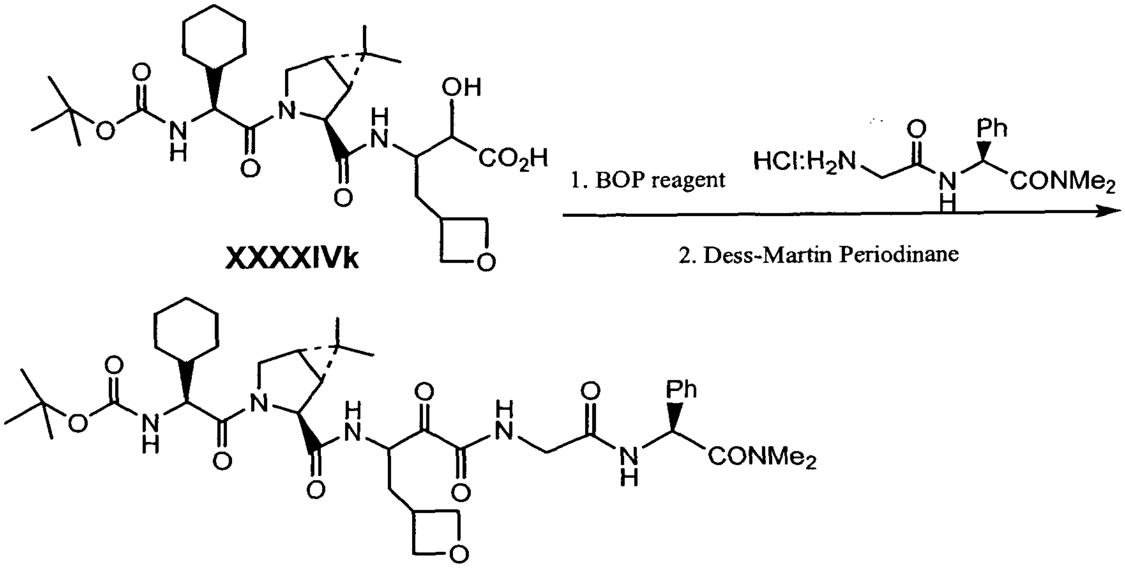
Step 9



XXXXIVj XXXXIVk

Potassium carbonate (0.054g; 0.39mmol) was added to the ester **XXXXIVj** (0.107g; 0.19mmol) in a mixture of methanol (3ml) and water (1ml) and the resulting reaction was stirred for a period of 16h. and partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried and concentrated to yield the acid **XXXXIVk** (0.099g).

Step 10



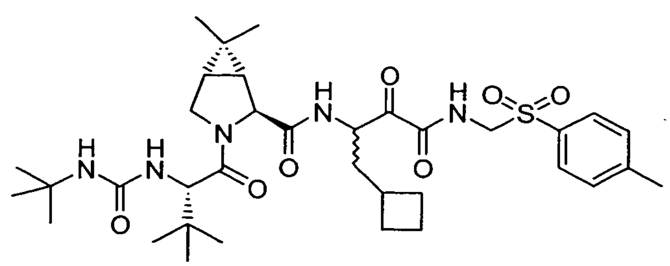
XXXXIVk

XXXXIV

Triethylamine (0.035ml; 0.25mmol) was added to a mixture of the carboxylic acid **XXXXIVk** (0.041g; 0.08mmol), the hydrochloride salt (0.023g; 0.08mmol) and BOP reagent (0.037g; 0.08mmol) in dichloromethane (3ml) and the resulting mixture was stirred at room temperature for a period of 4h. The reaction was partitioned between EtOAc and dilute aq. HCl (1M). The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated under reduced pressure.

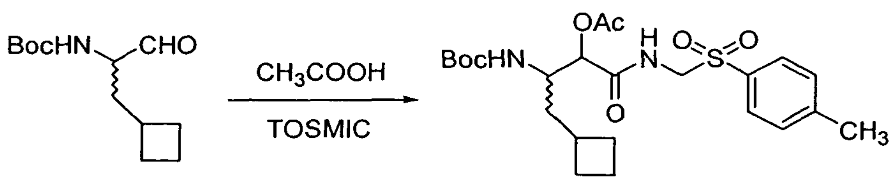
The residue from the aforegoing procedure was dissloved in dichloromethane (3ml) and Dess-Martin periodinane (0.065g; 0.15mmol) was added and the mixture stirred at room temperature for 2h. The reaction was partioned between 5% aq. sodium sulfite, sat. aq. sodium bicarbonate, water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2;MeOH; 20:1 as eluent to provide the alpha-keto amide **XXXXIV** (0.021g). FABMS: MH^+, 767.4.

Example XXXXVI Preparation of Compound of Formula XXXXVI



XXXXVI

Step 1

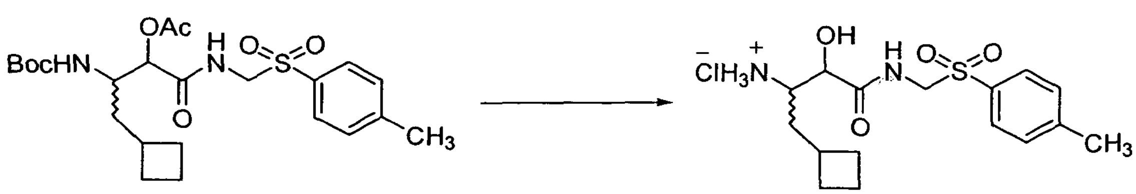


XXIIIe XXXXVIa

A solution of aldehyde **XXIIIe** (0.626 g, 2.75 mmol), TOSMIC (1.63 g, 8.27 mmol) and CH_3COOH (0.48 mL, 8.27 mmol) in dry CH_2Cl_2 (15 mL) was stirred at rt. for 36 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield 0.90 g (68%) of **XXXXVIa** as a colorless solid

MS (ES) *m/z*, relative intensity 965 [$(2M+1)^+$, 30], 483 [$(M+1)^+$, 53], 427 (60), 383 (100), 365 (71), 272 (64).

Step 2

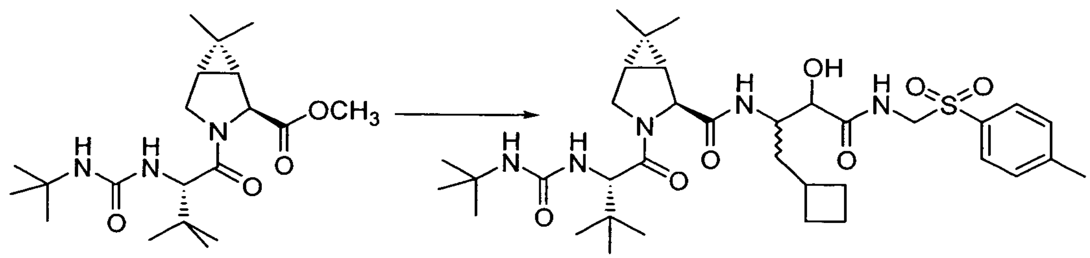


XXXXVIa XXXXVIb

A solution of **XXXXVIa** (0.9 g, 1.86 mmol) in HCl (30 mL, 6 M in CH_3OH, prepared by addition of acetyl chloride to CH_3OH at 0 °C) was stirred at rt. overnight. The reaction mixture was concentrated in *vacuo* and used as it is in the following step

MS (ES) *m/z*, relative intensity 681 [$(2M+1)^+$, 26], 341 [$(M+1)^+$, 100], 180 (40)

Step 3

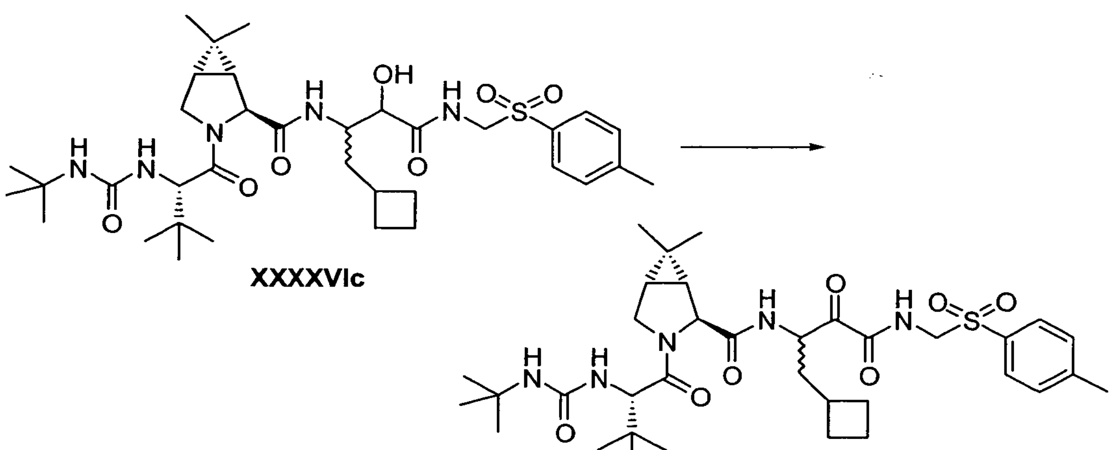


XXIVc **XXXXVIc**

The synthesis of **XXXXVIc** was accomplished using **XXIVc** (134 mg, 0.36 mmol), and amine **XXXXVIb** (120 mg, 0.32 mmol) following the procedure reported for example **XXIV** from **step 3** to yield product **XXXXVIc** which was used for further oxidation without purification

MS (ES) *m/z*, relative intensity 690 [$(M+1)^+$, 100], 591 (27), 537 (18), 513 (27), 478 (63), 438 (18), 414 (60), 268 (27)

Step 4



XXXXVIc

XXXXVI

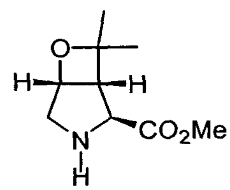
The synthesis of **XXXXVI** was accomplished by the oxidation of using alcohol **XXXXVIc** (219 mg, 0.32 mmol), EDCI (609 mg, 3.2 mmol), and $Cl_2CHCOOH$ (131 L, 1.59 mmol) following the procedure reported in example **XXIV, step 4** which

purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield product **XXXXVI** (117 mg, 53% over 2 steps) as a colorless solid.

MS (ES) *m/z*, relative intensity 688 [$(M+1)^+$, 32], 589 (81), 476 (100)

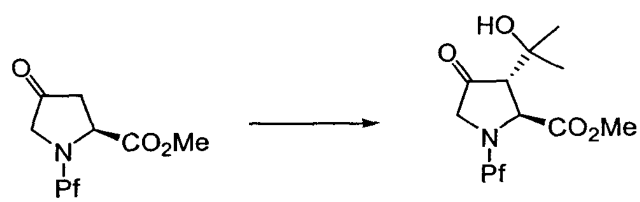
Synthesis of Intermediates

Example XXXXVII Preparation of intermediate of Formula XXXXVII



XXXXVII

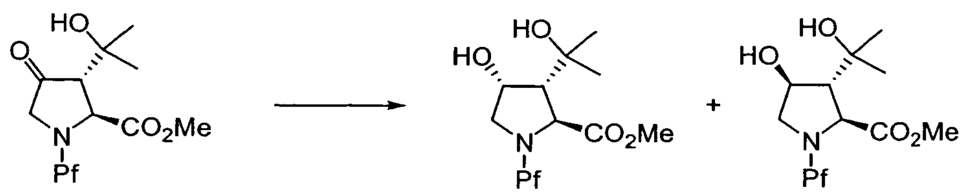
Step 1



XXXXVIIa XXXXVIIb

To the solution of ketone **XXXXVIIa** (4.93 g, 12.8 mmol) in anhydrous THF (100 mL) at -78 C was added a solution of lithium hexamethyldisilylazide (LiHMDS) (17.0 mL, 17.0 mmol). The resulting solution was stirred at that temperature for 1 h before a solution of acetone (1.51 mL, 20.5 mmol) and $BF_3 \cdot Et_2O$ (2.60 mL, 20.5 mmol) in THF (15 mL) was added. After stirred for another 4 h, 5% H_3PO_4 (20 mL) was added followed by saturated ammonium chloride solution (200 mL) and diethyl ether (200 mL). The layers were separated and aqueous layer was extracted with diethyl ether (2 X 200 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 20-50% EtOAc/hexane to give 1.84 g of **XXXXVIIb** (33%) and 3.26 g starting material **XXXXVIIa**

Step 2



XXXXVIIb XXXXVIIc XXXXVIId

To the solution of the ketone **XXXXVIIb** (0.94 g, 2.13 mmol) in anhydrous THF (20 mL) at -78 C was added a solution of $LiAlH_4$ in THF (2.6 mL, 2.6 mmol) and the reaction mixture was stirred for 40 min before $KHSO_4$ solution (1.0 M, 16 mL) was added. The mixture was allowed to warm to rt and to it was added EtOAc (100 mL) and water (50 mL). After the layers were separated and aqueous layer was extracted with EtOAc (2 X 50 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 30-100% EtOAc/hexane to give 0.49 g of **XXXXVIIc** (52%) and 0.18 g (19%) **XXXXVIId**.

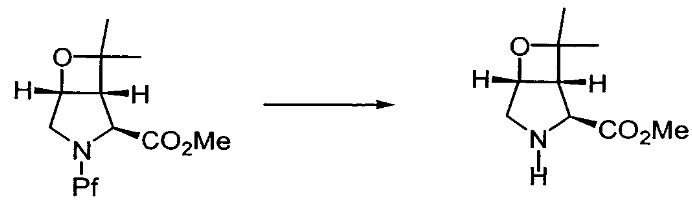
Step 3

XXXXVIIc XXXXVIIe

The solution of **XXXXVIIc** (103 mg, 0.232 mmol), triphenylphosphine (120 mg, 0.456 mmol) and diethyl azodicarboxylate (0.055 mL, 0.349 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 18 h. After concentrated in vacuo, the mixture

was purified by flash column chromatography using 10-30% EtOAc/hexane to give 24 mg (24 %) of **XXXXVIIe**.

Step 4

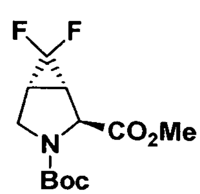


XXXXVIIe XXXXVII

The solution of **XXXXVIIe** in EtOH was hydrogenated at rt in the 10% Pd-C catalyst to **XXXXVII**.

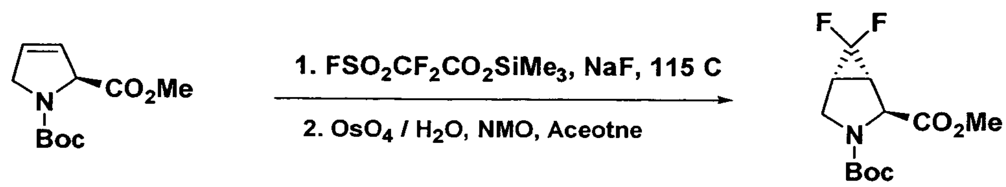
A number of inhibitors described in **table-6** using the intermediates **XXXXVII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example XXXXVIII Preparation of intermediate of Formula XXXXVIII



XXXXVIII

Step 1



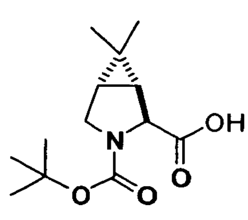
XXXXVIIIa

XXXXVIII

To 5g (22 mmol) of N-Boc-dehydroprolinemethylester **XXXXVIIIa** was added 25 mg of NaF and 2g of Toluene. At 110C, was added via syringe –pump 1.6equiv (35 mmol, 8.75g) of TMSfluorosulfonyldifluoroacetate (TFDA) in 1h. After 2h, reaction is cooled down to RT. To the mixture is added NMO(6.8g, 50 mmol), Acetone (50 mL), H2O (25 mL) and OsO4 (0.015 M in H2O, 1 mol%, 0.44 mmol, 28 mL). Reaction is stirred overnight at RT then diluted with EtOAc and washed with H2O and Brine. Organic layer was dried over MgSO4, filtered and concentrated to dryness. Purification by flash column chromatography (10 EtOAc, Hexane, silica) furnished Product **XXXXVIII** (0.76g).

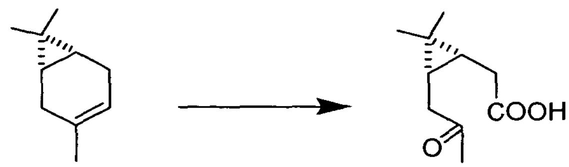
A number of inhibitors described in **table-6** using the intermediate **XXXXVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example IL Preparation of intermediate of Formula IL



IL

Step 1.(1R,3S)- 2,2-DIMETHYL-3-(2-OXOPROPYL)CYCLOPROPANEACETIC ACID .

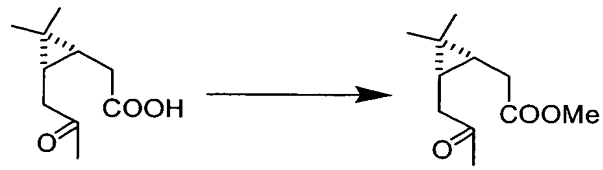


3-carene
ILa

ILb

A mixture of 0.55 L *tert*-butanol, 1.1 L water, 100 mL 3-carene **ILa** (Aldrich Chemical Co.), and 490 g $NaIO_4$, was treated with 2.2 g ruthenium chloride hydrate. The vigorously stirred mixture was alternately heated and cooled for 2 hr. to maintain a temperature of 35-40°C. The vigorously stirred mixture was alternately heated and cooled for another 1 hr. to maintain a temperature of 40-50°C. The vigorously stirred mixture was then heated for another 1/2 hr. to maintain a temperature of 50-55°C. The mixture was then cooled to 30°C, filtered on a Buchner funnel, and the precipitates were washed with 700 mL of *iso*-propyl ether. The aqueous portion of the filtrate was extracted with 900 mL of EtOAc-hexane (2:1), and the extract was combined with the ethereal portion of the filtrate. The combined organics were washed with 300 mL of 20% aqueous NaCl, then extracted with a solution of 36 g NaOH in 2.2 L water. The cooled aqueous extract was acidified with 100 mL of 12 N HCl and extracted with Et_2O (3 x 800 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to leave the title compound **ILb** 98 g (88%) as a gum. H^1NMR ($CDCl_3$) δ 2.39 (m, 2), 2.28 (m,2), 2.19 (s, 3), 1.1.12 (s, 3), 0.90 (m, 2), 0.63 (s, 3).

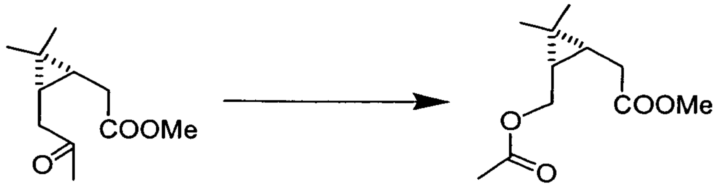
Step 2. (1R,3S)-METHYL 2,2-DIMETHYL-3-(2-OXOPROPYL)CYCLOPROPANEACETATE.



ILb ILc

A solution of 98 g of **ILb**, the product of the preceding step and 0.55 L DMF was treated with 98 g Cs_2CO_3. The mixture was stirred for 10 minutes, 41.5 mL MeI was added, and the mixture was stirred at 40°C for 1 hr. The mixture was cooled and filtered on a Buchner funnel. The filtrate was quenched with 2.5 L of 18% aqueous NaCl, the organic layer was separated, and the aqueous solution was extracted with Et_2O-hexane (1:1; 2 x 1 L). The combined organic layer and extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave the title compound **ILc** as 91 g (86%) thick oil. H^1NMR ($CDCl_3$) δ 3.67 (s, 3), 2.3 (m, 4), 2.17 (s, 3), 1.12 (s, 3), 0.97 (m, 2), 0.91 (s, 3).

Step 3. (1R,3S)-METHYL 3-(ACETOXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE.

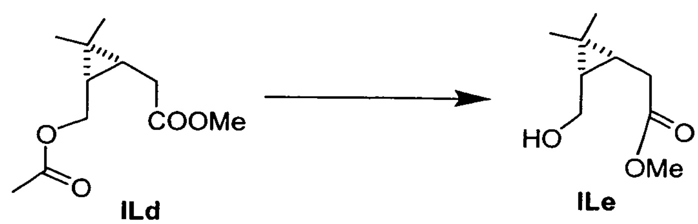


ILc ILd

A solution of **ILc** 91 g of the product of the preceding step and 0.7 L 1,1,2-trichloroethane was treated with 165 g of 70% *m*-chloroperbenzoic acid. The

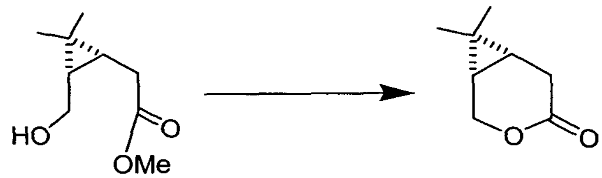
mixture was stirred at ambient temperature for 1 hr, then heated with an oil bath to maintain a reaction temperature of 65-70°C for 1 hr., and then heated at 75°C for 1 hr. more. The mixture was cooled, filtered on a Buchner funnel, and the filter cake was washed with fresh trichloroethane. The combined filtrate and washings were concentrated *in vacuo* to 0.5 L, and the residue was diluted with 2.5 L of hexane-Et_2O (3:1). The organic solution was washed repeatedly with a solution of 3.5% aqueous K_2CO_3-brine (3:1; 8 x 0.9 L), then with brine, then dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave the title compound **ILd** as 98 g (100%) thick oil. H^1NMR ($CDCl_3$) δ 4.1-3.9 (m, 2), 3.68 (s, 3), 2.34 (d, 2), 2.04 (s, 3), 1.12 (s, 3), 1.04 (m, 2), 1.00 (s, 3).

Step 4. (1R,3S)-METHYL 3-(HYDROXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE



A solution of 98 g **ILd** of the product of the preceding step and 1 L methanol was treated with 19 g K_2CO_3, and the mixture was stirred at 30°C for 1 hr. The mixture was concentrated *in vacuo* to remove 0.6 L methanol, the residue was quenched with cold 10 % aqueous KH_2PO_4, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave 70 g (89%) of the title compound **ILe** as a gum. H^1NMR ($CDCl_3$) δ 3.80 (q, 1), 3.73 (s, 3), 3.52 (m, 1), 2.68 (d of d, 1), 2.23 (d of d, 1), 1.09 (s, 3), 1.1-0.9 (m, 2), 0.98 (s,3).

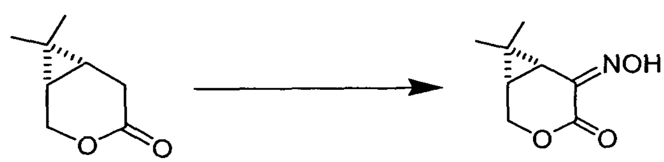
Step 5. (1S,6R)-7,7-DIMETHYL-3-OXABICYCLO[4.1.0]HEPTAN-4-ONE.



ILe ILf

A solution of **ILe** 70 g of the product of the preceding step and 1.1 L xylenes was treated with 30.8 g DBU. The solution was heated to a gentle reflux for 18 hr. as methanol was removed from the distillate. The solution was cooled, washed with cold 1 N HCl, then with brine; dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo.* The residue was chromatographed on 600 g silica gel using a gradient of CH_2Cl_2 to 1:10 EtOAc-CH_2Cl_2 to obtain the title compound **ILf** as 54 g (94%) oil. H^1NMR ($CDCl_3$) δ 4.71 (d of d, 1), 4.04 (d of d, 1), 2.75 (d of d, 1), 2.16 (d of d, 1), 1.16 (s, 3), 1.25 (m, 1), 1.12 (s, 3).

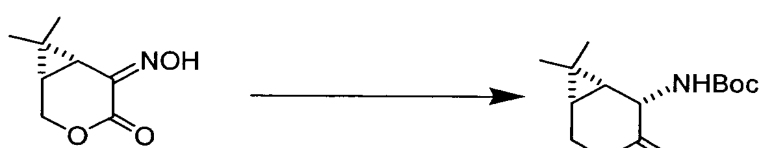
Step 6. (1S,6R,5E)-7,7-DIMETHYL-3-OXABICYCLO[4.1.0]HEPTANE-4,5-DIONE, 5-OXIME.



ILf ILg

A solution of 42 g of the product of the preceding step **ILf** and 300 mL anhydrous toluene was treated with 102 mL of 90% *tert*-butylnitrite. The stirred mixture was alternately heated and cooled as needed as 45 g potassium *tert*-butoxide was added in 6 portions over 20 minutes at 30-35°C. Then 180 mL of anhydrous methanol was added, the temperature raised to 40°C, and stirring continued at 40°C for 2.5 hr. The mixture was cooled, quenched with a cold solution of 1.1 L of 10% aqueous and 20 mL 12N HCl, then extracted with EtOAc-toluene (3:1). The extracts were washed with 5% aqueous $NaHCO_3$, then brine; dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue (25 g) was chromatographed on 150 g silica gel using a gradient of CH_2Cl_2 to 35:65 EtOAc-CH_2Cl_2 to obtain 15 g (29%)of the title compound **ILg** as an oil. H^1NMR ($CDCl_3$) δ 4.82 (d of d, 1), 4.55 (d of d, 1), 2.40 (d, 1), 1.49 (m, 1), 1.27 (s, 3), 1.18 (s, 3).

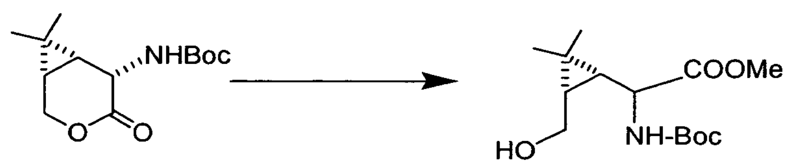
Step 7.



ILg **ILh**

A solution of 18 g of the product of the preceding step **ILg** and 400 mL EtOAc was treated with 32 g di-*tert*-butyldicarbonate (Boc_2O), and 2.0 g of 10% Pd on carbon. The mixture was hydrogenated at 2.5 atm for 18 hr, filtered, and the filtrate evaporated to leave 36 g of the title compound mixed with Boc_2O, which was taken directly to the next step. A portion was chromatographed to obtain **ILh** as pure title compound: H^1NMR (DMSO-d_6) δ 7.28 (d, N<u>H</u>), 4.76-4.64 (m, 2), 4.44 (d, 1), 1.40 (s, 9), 1.24 (m, 1), 1.11 (m, 2), 1.07 (s, 3), 0.99 (s, 3).

Step 8. (1R,3S)-METHYL ALPHA(S)-[[(1,1-DIMETHYLETHOXY)CARBONYL]AMINO]-3-(HYDROXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE



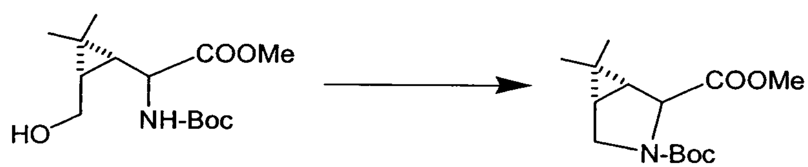
ILh **ILi**

A solution of 35 g of **ILh** the product mixture of the preceding step and 350 mL anhydrous methanol was treated with 12 g of finely ground anhydrous K_2CO_3. The mixture was vigorously stirred for 2 hr., concentrated *in vacuo* with a 25°C bath, and then quenched with 0.6 L of 10% aqueous KH_2PO_4. The solution was extracted with EtOAc-hexane (95:5; 2 x 200 mL), the extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated *in vacuo* to leave **ILi** 22 g (70%) of the title compound as a gum mixture of the two epimers in an α-*S*/α-*R* ratio of 8:2, which did not have to be separated for the present purpose. A portion was chromatographed with Et_2O-hexane (60:40) to obtain pure α-*S* -epimer of the title compound: H^1NMR ($CDCl_3$) δ 5.2 (br s, 1), 4.05 (br s, 1), 3.81 (m, 1), 3.76 (s, 3), 3.65 (m, 1), 1.43 (s, 9), 1.14 (s, 3), 1.06 (s, 3), 1.05 (m, 1), 0.86 (m, 1). Optical rotation: $[\alpha]_D^{25}$ – 62.9° (c=1, MeOH). Elemental analysis: theory C 58.52, H 8.77, N 4.87; found C 58.48, H 8.75, N 5.10...

Further elution provided the α-*R*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.95 (br d, 1), 4.03 (m, 1), 3.82 (m, 1), 3.78 (s, 3), 3.71 (m, 1), 1.44 (s, 9), 1.13 (m, 1), 1.10 (s, 3), 1.08 (s, 3), 0.86 (m, 1). Optical rotation: $[\alpha]_D^{25}$ –

32.8° (c=1, MeOH). Elemental analysis: theory C 58.52, H 8.77, N 4.87; found C 58.46, H 8.69, N 4.74.

Step 9. (1R,5S)-6,6-DIMETHYL-,3-AZABICYCLO[3.1.0]HEXANE-2(S),3-DICARBOXYLIC ACID 3-(1,1-DIMETHYLETHYL) 2-METHYL ESTER



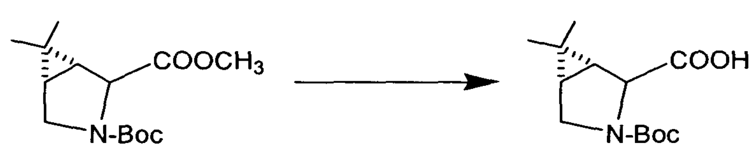
ILi **ILj**

A solution of 21.6 g triphenylphosphine and 250 mL anhydrous THF was cooled to –10 °C and treated dropwise with 16.2 g diisopropylazodicarboxylate as the temperature of the reaction rose to +5 °C. After 5 minutes additional stirring, the mixture was treated a solution of 19.7 g of **ILi** the product mixture of the preceding step in 35 mL THF. After 10 minutes additional stirring, the mixture was heated at reflux for 3 hr., cooled, and evaporated *in vacuo*. The residue was transferred to a separatory funnel with a total of 450 mL of methanol-water (1:1), and he 2 phase mixture was extracted with hexane (7 x 225 mL). The combined extracts were washed with 20 mL of methanol-water (1:1), then brine; dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated *in vacuo*. The residue was taken up in 400 mL hexane, suction-filtered through a pad of 30 g silica gel, and the silica pad was eluted with an additional 210 mL of EtOAc-hexane (1:9). The combined filtrates were evaporated *in vacuo* to leave 12.8 g (69%) of the title compound **ILj** as a gum mixture of 2 epimers, contaminated with a small amount of diisopropylhydrazinedicarboxylate, but suitable for the subsequent reactions.

The pure *S*-epimer of the preceding step was treated in the same fashion to afford the pure *S*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.21 and 4.09 (s+s, 1), 3.75 (s, 3), 3.65 (m, 1), 3.41 (m, 1), 1.44 and 1.39 (s+s, 9), 1.38 (m, 2), 1.03 (s, 3), 0.98 and 0.97 (s+s, 3). Elemental analysis: theory C 62.43, H .8.61, N 5.20; found C 61.82, H 8.67, N 5.15.

The *R*-epimer of the preceding step was treated in the same fashion to afford the *R*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.49 and 4.30 (d+d, 1), 3.62 (s, 3), 3.59 (m, 1), 3.42 (m, 1), 1.65 (m, 1), 1.45 and 1.39 (s+s, 9), 1.36 (m, 1), 1.10 (s, 3), 0.99 (s, 3).

Step 10.



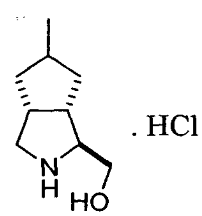
ILj **IL**

A solution of 14.5 g of the product mixture **ILj** of the preceding step and 270 mL 1,4-dioxane was treated with 135 mL of 1M aqueous LiOH, and the mixture was heated at 80°C for 4 hr. The mixture was cooled, concentrated *in vacuo* to half volume, diluted with 200 mL water, and extracted with hexane. The aqueous layer was chilled and treated with a solution of 9 ml of 12N HCl in 50 mL of 10% aqueous KH_2PO_4, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated *in vacuo* to leave the title compound **IL** as 10.8 g (78%) gum, > 90% chemically and diasteriomerically pure by PMR, and suitable for subsequent synthesis: H^1NMR ($CDCl_3$) δ 4.20 and 4.11 (s+s, 1), 3.62 (m, 1), 3.44 (m, 1), 1.68 and 1.45 (d+unk,

1), 1.46 and 1.40 (s+s, 9), 1.45 (m buried under 1.46, 1), 1.07 (s+s, = 2 Hz, 3), 0.99 and 0.95 (s+s, 3).

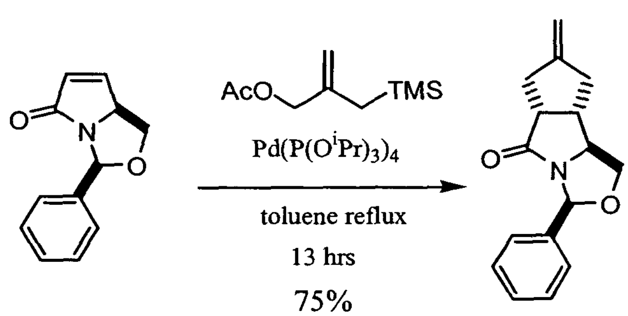
A number of inhibitors described in **table-6** using the intermediates **IL** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example L Preparation of intermediate of Formula L



L

Step 1

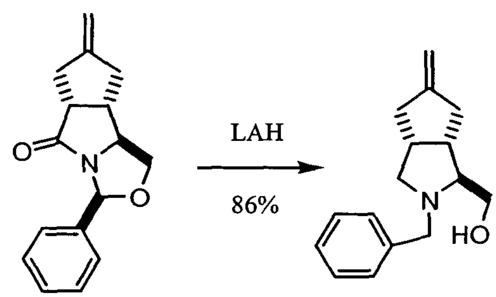


La **Lb**

To a mixture of **La** (10.0 g, 50.0 mmole), 2-[(trimethylsilyl) methyl]-2-propanen-1-yl acetate (22.0 g, 118 mmole) and triisopropyl phosphite (18.6 g, 89.2 mmole) in toluene (50 ml) was added palladium (II) acetate (2.5 g, 11 mmole)

with stirring at room temperature under an Ar atmosphere. It was heated to 120 °C (oil bath) for thirteen hours. Cooling down to room temperature followed by flash chromatography (CH_2Cl_2: Hexane = 4:1) provided 9.55 gram of **Lb** (75%). $[\ ]^{25}$ = +132 ° ($CHCl_3$). HRMS (FAB) Calcd for $C_{16}H_{18}NO_2$ (MH+): 256.1338; found: 256.1340.

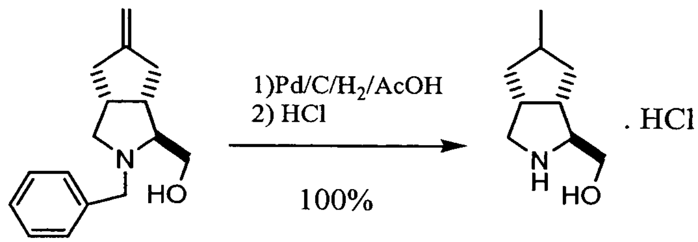
Step 2



Lb **Lc**

To a solution of **Lb** (2 g, 7.8 mmol) in anhydrous THF (50 ml) was added LAH (1.13g, 28.9 mmol) in small portions at 0 °C. The mixture then refluxed for six hours before cooled to 0 °C. To the reaction were carefully added 2ml of H_2O, 2ml of 15% NaOH and 6 ml of H_2O. The solid was removed by filtration and the concentrated filtrate was chromatographed (2% MeOH in CH_2Cl_2) to give 1.33 gram of **Lc** (70%). HRMS (FAB) Calcd for $C_{16}H_{22}NO$ (MH+): 244.1701; found: 244.1697.

Step 3

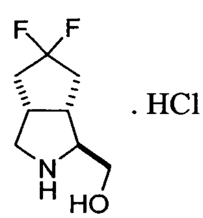


Lc L

A mixture of compound **Lc** (1.33 g, 5.46 mmol) and 10% Pd on carbon (1.3 gram) in acetic acid (20 ml) was hydrogenated under 60 psi for three days. The catalyst was filtered off and the filtrate was concentrated in vacuum. The residue was dissolved in 20 ml of 4N HCl in dioxane and the solution was evaporated to dryness. Compound **L** was obtained in 1.04 gram (100%) as a 1: 1 mixture of two epimers. HRMS (FAB) Calcd for $C_9H_{18}NO$ (MH+): 156.1388; found: 156.1390.

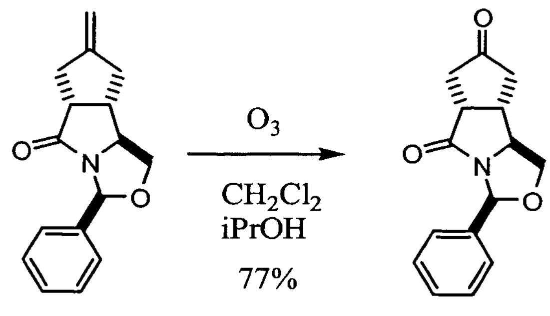
A number of inhibitors described in **table-6** using the intermediates **L** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX, and XXXX**

Example LI Preparation of intermediate of Formula LI



LI

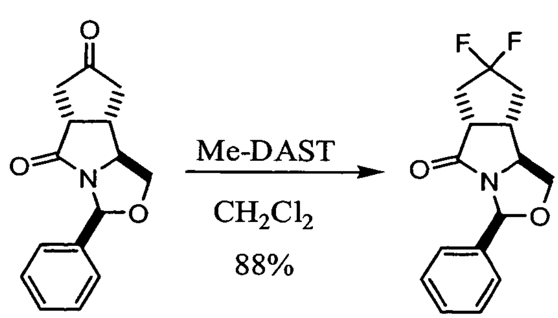
Step 1



Lb **LIa**

Compound **Lb** (2.6 g, 10.2 mmol) in a mixture of CH_2Cl_2 (30 ml) and ^iPrOH (10 ml) was ozonized at –78 °C until a bluish color persisted (Ca. 40 minutes). Dimethyl sulfide (10 ml) was added and the solution was stirred at room temperature over night. The solvent was removed in vacuum and the residue was partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (2% MeOH in CH_2Cl_2) provided 2.32 gram of **LIa** (77%). MS (MH+, FAB) = 257.

Step 2

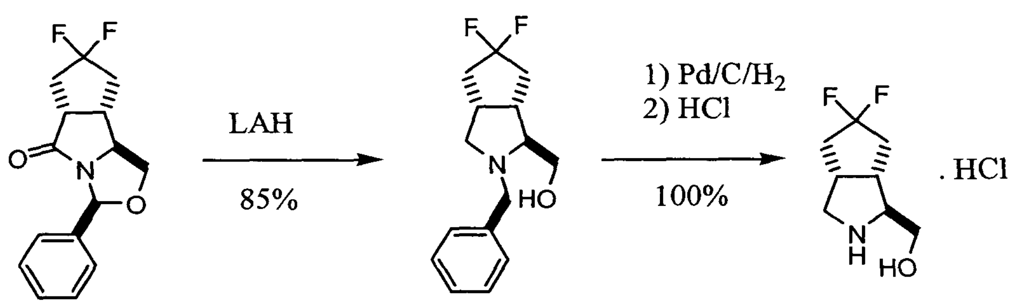


LIa **LIb**

To a solution of **LIa** (0.86 g, 3.35 mmol) in dry CH_2Cl_2 (30 ml) was added dimethylaminosulfur trifluoride (methyl DAST, 2.23 g, 16.8 mmol) at room temperature. The solution was stirred at room temperature for two days. It was

carefully added to a mixture of ice and saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed (0.8 % of MeOH in CH_2Cl_2) to give **LIb** (0.82 g, 88%). HRMS (FAB) Calcd for $C_{15}H_{16}NO_2F_2$ (MH+): 280.1149; found: 280.1152.

Step 3

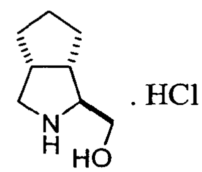


LIb LIc LI

By following the same procedures as described for the preparation of **L** from **Lb** through **L** 0.44 gram of **LIb** provided 0.31 gram of **LI** (92% in two steps). . HRMS (FAB) Calcd for $C_8H_{14}NOF_2$ (MH+): 178.1043; found: 178.1042.

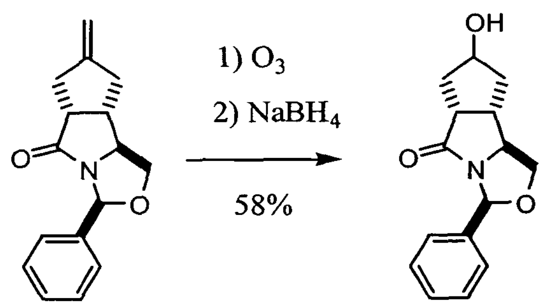
A number of inhibitors described in **table-6** using the intermediates **LI** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX, and XXXX**

Example LII Preparation of intermediate of Formula LII



LII

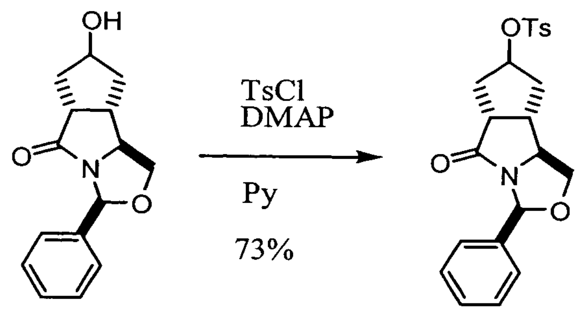
Step 1



Lb LIIa

Compound **Lb** (3.74 g, 14.7 mmol) in CH_2Cl_2 (30 ml) was ozonized at –78 °C until a bluish color persisted (Ca. 60 minutes). It was purged with N_2 for 5 min, and was added to a cold solution of $NaBH_4$ (4.44g, 117 mmol) in 50 ml of EtOH/H2O (1: 1). It was stirred for 12 hrs at RT then extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed (2% MeOH in CH_2Cl_2) to give **LIIa** (2.19 g, 58%). HRMS (FAB) Calcd for $C_{15}H_{18}NO_3$ (MH+): 260.1287; found: 260.1283.

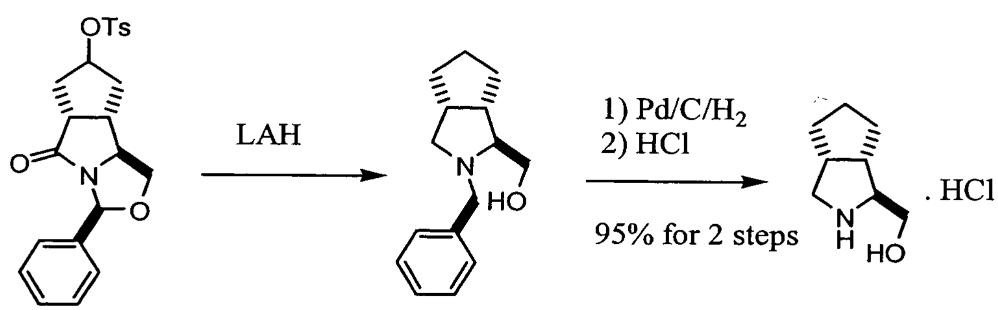
Step 2



LIIa **LIIb** .

To a solution of **LIIa** (2.18 g, 8.40 mmol) in dry pyridine (50 ml) were added toluenesulfonyl chloride (3.2 g, 16.8 mmol) and N, N-dimethylaminopyridine (1.03 g, 8.40 mmol). It was stirred at RT for 3 days and concentrated in vacuum. The residue was partitioned between 3% citric acid and EtOAc. The organic layer was washed with 3% citric acid again, followed by brine. After removing the solvent the residue was chromatographed to provide **LIIb** (2.54 g, 73%). HRMS (FAB) Calcd for $C_{22}H_{24}SNO_5$ (MH+): 414.1375; found: 414.1378.

Step 3

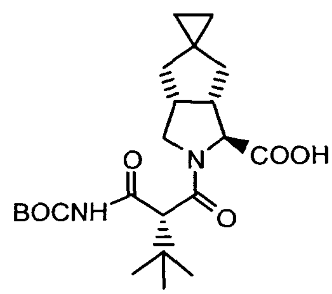


LIIb **LIIc** **LII**

By following the same procedures as described for the preparation of **L** from **Lb** through **L,** 2.53 gram of **LIIb** provided 1.03 gram of **LII** (95% in two steps). HRMS (FAB) Calcd for $C_8H_{16}NO$ (MH+): 142.1232; found: 142.1233.

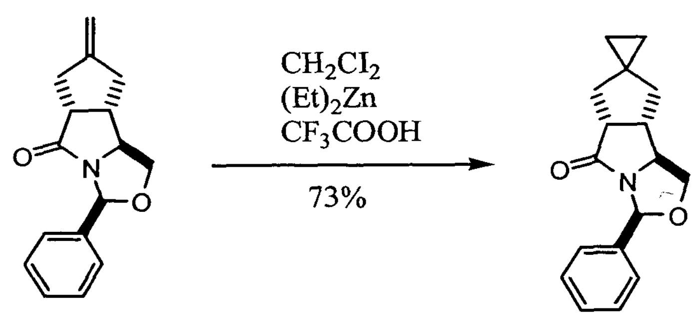
A number of inhibitors described in **table-6** using the intermediates **LII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LIII Preparation of intermediate of Formula LIII



LIII

Step 1

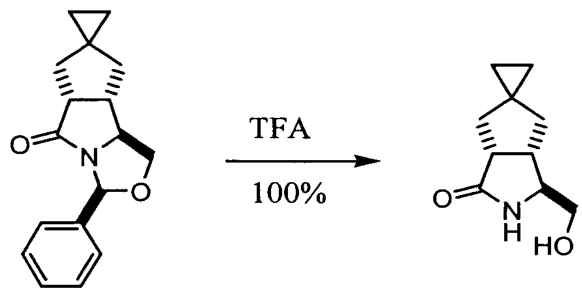


Lb **LIIIa**

To 7.84 mmol of diethyl zinc (I N in hexane) in dry CH_2Cl_2 (30 ml) was added trifluoroacetic acid (0.893 g, 7.84 mmol) dropwise at 0 °C. Upon stirring for an additional 20 min diiodomethane (2.10 g, 7.84 mmol) was added, followed by **Lb** (1 g, 3.92 mmol) in 5 ml of CH_2Cl_2 in 20 min. The ice bath was removed and the mixture was stirred at RT for 14 hours. The reaction was quenched by saturated NH4Cl and extracted with EtOAc. The EtOAc solution was washed with

saturated Na_2SO_4, followed by brine and concentrated in vacuum. The residue was chromatographed to provide **LIIIa** (4.61 g, 73%). HRMS (FAB) Calcd for $C_{17}H_{20}NO_2$ (MH+): 270.1494; found: 270.1497.

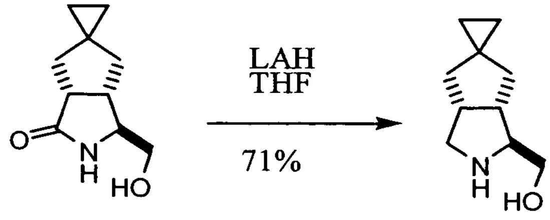
Step 2



LIIIa **LIIIb**

Trifluoroacetic acid (TFA, 10 ml) was added to a solution of **LIIIa** (4.6 g, 17.1 mmol) in THF (20 ml) and H_2O (20 ml) at RT. After stirring overnight the solvents were removed in vacuum. The residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous phase was back extracted with EtOAc five times. The combined organic phase was dried over Na_2SO4 and concentrated. The residue was chromatographed to give **LIIIb** (3.1 g, 100%). HRMS (FAB) Calcd for $C_{10}H_{16}NO_2$ (MH+): 182.1181; found: 180.1182.

Step 3

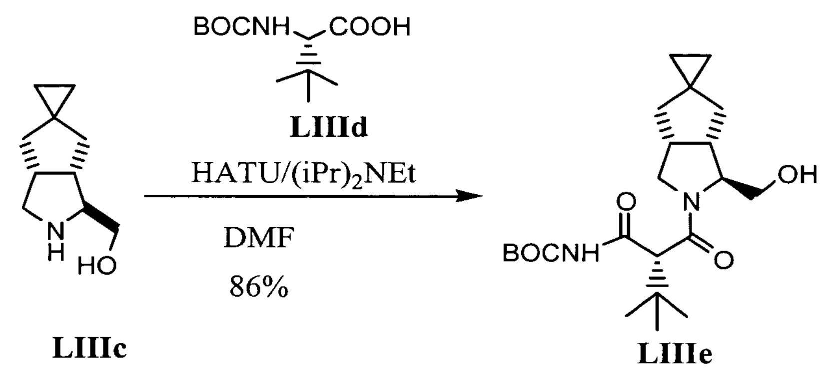


LIIIb **LIIIc**

LAH (1.76 g, 46.3 mmol) was added to **LIIIb** in dry THF (50 ml) in small portions at 0 °C. The mixture then refluxed for six hours before cooled to 0 °C. To the reaction were carefully added 2ml of H_2O, 2ml of 15% NaOH and 6 ml of H_2O. The solid was removed by filtration and the concentrated filtrate was chromatographed (30% MeOH in CH_2Cl_2 with 1% NH_4OH) to give 0.39 gram of **LIIIc** (71%). HRMS (FAB) Calcd for $C_{10}H_{18}NO$ (MH+): 168.1388; found: 168.1389.

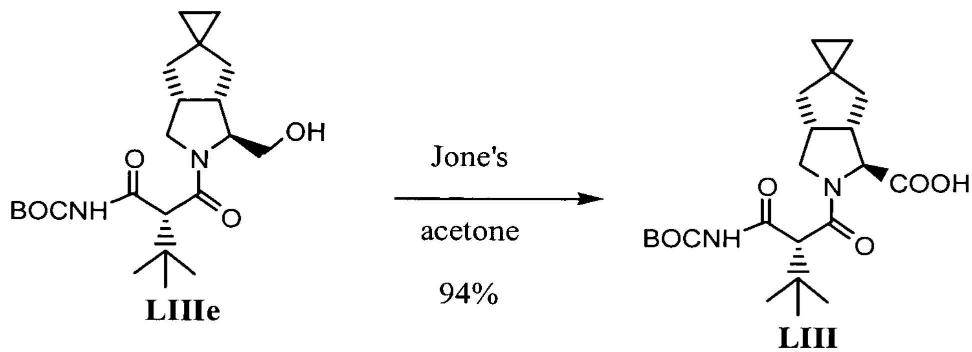
Step 4

.



To a mixture of **LIIIc** (0.5 g, 2.99 mmol), **LIIId** (0.69 g, 2.99 mmol) and HATU (1.14 g, 3 mmol) in dry DMF (20 ml) was added N, N-diisopropylethylamine (1 ml, 5.89 mmol)) at 0 °C. It was stirred at RT for 3 hrs. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was successively washed with 3% citric acid, saturated $NaHSO_4$ and brine, dried over Na2SO4 and concentrated. The product **LIIIe** (0.978g, 86%) thus obtained was sufficiently pure for the next step. HRMS (FAB) Calcd for $C_{21}H_{37}N_2O_4$ (MH+): 381.2910; found: 381.2749.

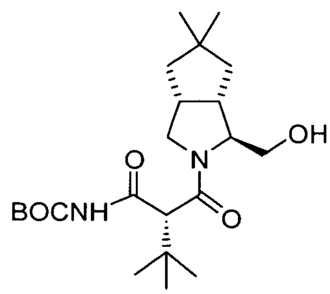
Step 5



To a solution of **LIIIe** (0.49 g, 1.29 mmol) in acetone (20 ml) was added Jone's reagent (2 ml of 2.5 M solution, 5 mmol) at 0 °C. It was stirred at 0 °C for 20 min, then at RT for 30 hrs. To this mixture were successively added EtOAc (50 ml), anhydrous Na_2SO_4 (3 g), celite (2g) and ^iPrOH (1 ml). It was stirred vigorously for 20 min. The solid was filtered off. The filtrate was washed with 3% citric acid, dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed (3% MeOH in CH_2Cl_2, 0.5% acetic acid) to provide **LIII** (0.48 g, 94%). HRMS (FAB) Calcd for $C_{21}H_{35}N_2O_5$ (MH+): 395.2546; found: 395.2543.

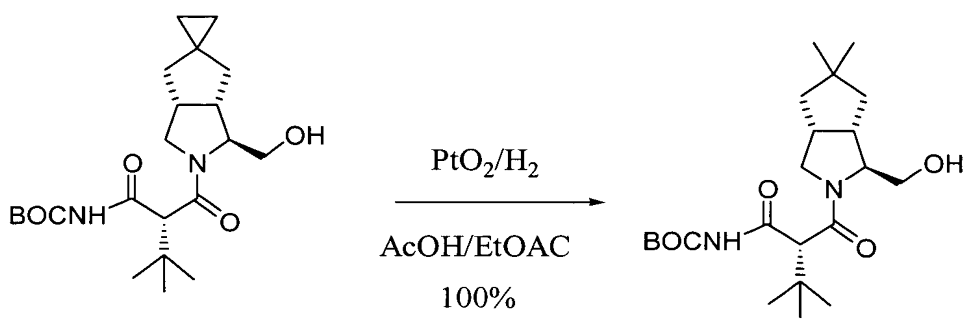
A number of inhibitors described in **table-6** using the intermediates **LIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

__Example LIV Preparation of intermediate of Formula LIV__



LIV

Step 1

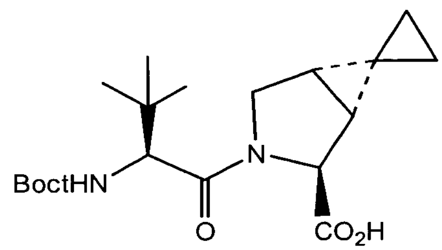


LIIIe **LIV**

Compound **LIIIe** (0.41 g, 1.08 mmol) in a mixture of solvent of AcOH (10 ml) and EtOAc (20 ml) containing PtO_2 (1 g) was hydrogenated under 1 atm of H_2 for 3 hrs. The catalyst was removed by filtration and the filtrate was concentrated in vacuum to provide **LIV** (0.41g, 100%). HRMS (FAB) Calcd for $C_{21}H_{39}N_2O_5$ (MH+): 383.2910; found: 383.2906.

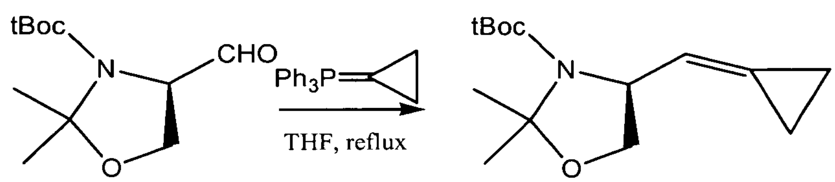
A number of inhibitors described in **table-6** using the intermediates **LIV** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

<u>**Example LV Preparation of intermediate of Formula LV**</u>



LV

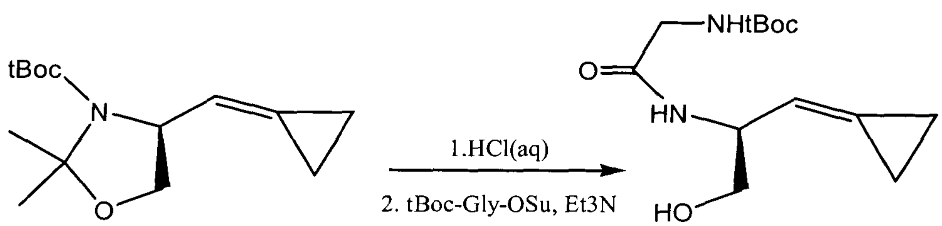
Step 1



LVa **LVb**

Potassium bis(trimethylsilyl)amide (158ml of a 0.5M solution in toluene; 79mmol) was added to a stirred suspension of cyclopropyltriphenylphosphonium bromide (33.12g; 86.4mmol) in anhydrous tetrahydrofuran (130ml) and the resulting orange mixture was stirred under an atmosphere of nitrogen at room temperature for a period of 1h., before the addition of the aldehyde **LVa** (9.68g; 42.2mmol) in THF (8ml). The reaction was then refluxed under an atmosphere of nitrogen for a period of 2h. After cooling, methanol, diethyl ether and Rochelles salt were added. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using EtOAc-hexane (1:99) to EtOAc-hexane (5:95) to provide the alkene **LVb** (8.47g) as a yellow oil.

Step 2

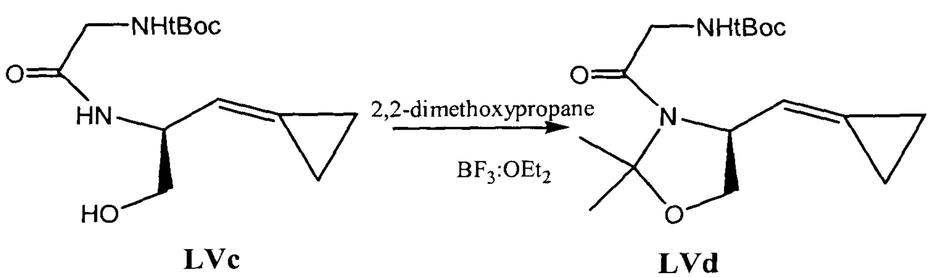


LVb **LVc**

A solution of 1M HCl in MeOH/MeOAc was prepared by adding14.2ml of acetylchloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.
The carbamate **LVb** (9.49g; 37.5mmol) was dissolved in methanol (12ml) and added to 1M HCl in MeOH/MeOAc (150ml) while cooled in an ice bath. The resulting mixture was maintained at this temperature for 1h., then the ice bath was removed and stirring continued overnight at room temperature. The volatiles were removed under reduced preesure to yield a yellow oil which was used in the next step without purification.

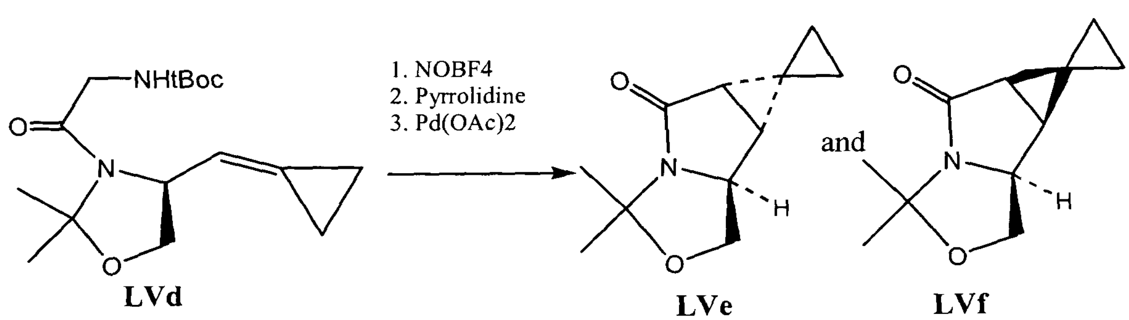
The yellow oil is dissolved in a mixture of THF (30ml) and MeOH (20ml) and treated with triethylamine (15ml; 108mmol) until the solution was pH=9-10. After placing in an ice bath, the mixture was treated with N-Boc-Gly-OSu (11.22g; 41mmol). The icebath was withdrawn and the reaction stirred at room temp. for 1h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methanol (1-3%) in dichloromethane providing the desired amide **LVc** (9.09g).

Step 3



The alcohol **LVc** (9.09g; 33.6mmol) was dissolved in acetone (118.5ml) and treated with 2,2-dimethoxypropane (37.4ml;304mmol) and BF_3:Et2O (0.32ml; 2.6mmol) and the resulting mixture was stirred at room temperature for a period of 5.5h The reaction solution was treated with a few drops of triethylamine and the volatiles were removed under reduced pressure.The residue was purified by silica gel column chromatography using 5-25% EtOAc in hexanes to provide the N,O-acetal **LVd** (8.85g).

Step 4

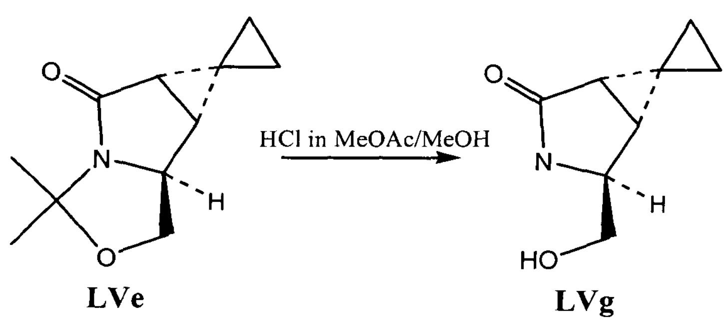


The carbamate **LVd** (8.81g; 28.4mmol) was dissloved in acetonitrile (45ml) and the solution was cooled to –40C under an atmosphere of nitrogen. Pyridine (6.9ml; 85.3mmol) followed by nitrosium tetrafluoroborate (6.63g; 56.8mmol) were added and the resulting reaction mixture maintained below 0C until TLC indicated

that no starting material remained (approx. 2.25h.). Pyrrolidine (20ml; 240mmol) was added and the cooling bath was withdrawn and stirring was continued at room temperature for 1h. and then the volatiles were removed under reduced pressure. The residue was quickly passed through a pad of silica gel to provide a yellow oil.

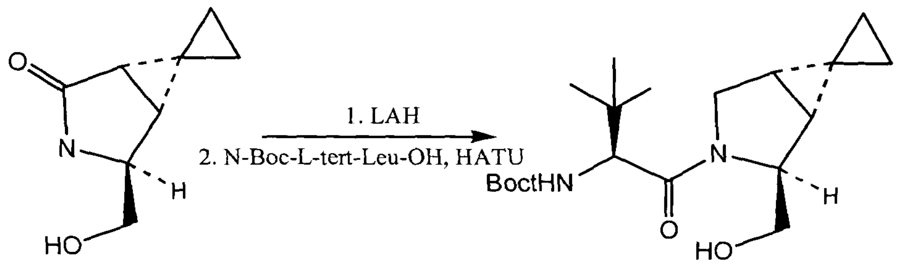
.The yellow oil was dissolved in anhydrous benzene (220ml) and palladium acetate (0.317g; 1.41mmol) was added before heating the resulting mixture to reflux, under an atmosphere of nitrogen for a period of 1.5h. After cooling, the volatiles were removed under reduced pressure and the dark residue was purified by silica gel column chromatography using EtOAc-hexane (1:4) to provide the I) the trans- pyrrolidinone **LVe** (1.94g) followed by ii) the cis-pyrolidinone **LVf** (1.97g).

Step 5



Freshly prepared 1M HCl in MeOAc/MeOH (10ml; as described above) was added to the N,O-acetal **LVe** and stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using 0-4%MeOH in dichloromethane as eluent to provide the desired alcohol **LVg** (1.42g), a yellow oil.

Step 6

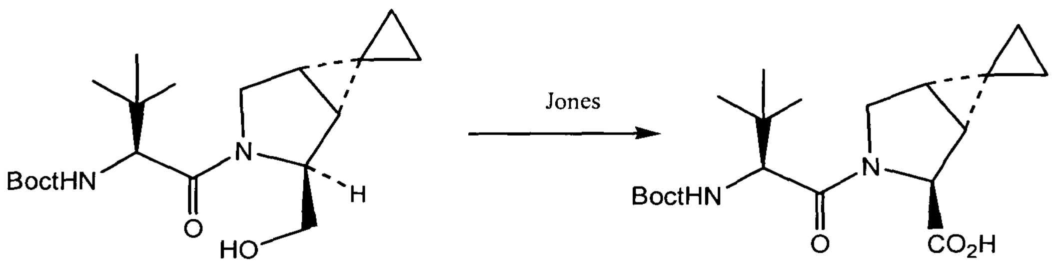


LVg LVh

To a solution of the lactam **LVg** (1.29g; 8.44mmol) in anhydrous tetrahydrofuran (55ml) was added lithium aluminum hydride (2.40g; 63.2mmol) and the resulting mixture was refluxed for 8h. After cooling, water, followed by 15% aq. NaOH were added and the resulting mixture was filtered through celite and the solid was washed thoroughly with THF and MeOH. The solvent was removed under reduced pressure and the residue redisolved in dichloromethane, dried and concentrated under reduced pressure to provide the pyrrolidine, used without purification.

Hunigs base (4.5ml; 25.8mmol) was added to a mixture of N-Boc-L-tert-Leu-OH (1.76g; 7.6mmol), The crude pyrrolidine and HATU (2.89g; 7.6mmol) in anhydrous dichloromethane (50ml) at –60C, under an atmosphere of nitrogen. The resulting reaction was allowed to come to room temperature slowly, overnight. EtOAc was added and the yellow solution was washed with dil.aq. HCl, sat. aq. sodium bicarbonate, water, brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:3) to give the desired amide **LVh** (2.00g).

Step 7

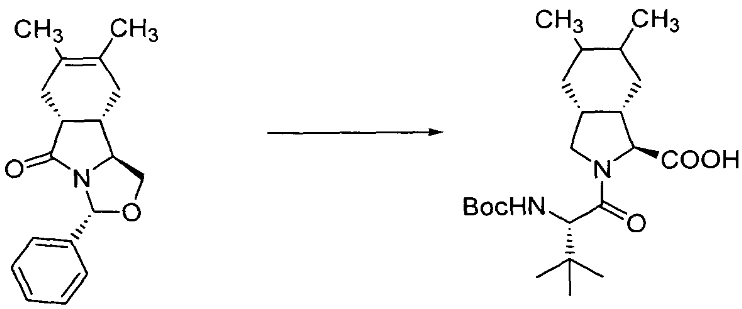


LVh LV

The alcohol **LVh** (2.00g; 5.67mmol) was dissolved in acetone (116ml) and cooled in an ice bath for 10min. This solution was then added to a cooled Jones reagent (14.2ml; approx 2mmol/ml) and the resulting mixture was stirred at 5C for 0.5h and the cooling bath was removed. The reaction was stirred for a further 2h. at room temp., before adding to sodium sulfate (28.54g), celite (15g) in EtOAc (100ml). Isopropanol (15ml) was added after 1min and then stirred for a further 10min. and filtered. The filtrate was concentrated under reduced pressure, providing a brown oil which was dissolved in EtOAc. This solution was washed with water, 3% aq. citric acid, brine, dried and concentrated to provide the desired carboxylic acid **LV** (1.64g) as a white solid.

NOTE: Alternatively XXIVc- acid, XXVIg-acid, XXVIIc, could be synthesized following the procedure mentioned above in good yields. A number of inhibitors described in **table-6** using the intermediates **LV** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

<u>**Example LVI Preparation of intermediate of Formula LVI**</u>

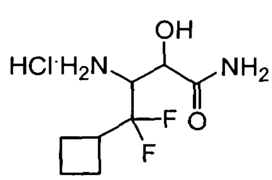


LVIa **LVI**

The synthesis of **LVIa** was accomplished following the procedure reported in Bailey, J, H.; Cherry, D, T.; Crapnell, K, M.; Moloney, M. G.; Shim, S. B.; Bamford, M. J.; Lamont, R. B. Tetrahedron (1997), 53, 11731. This was converted to **LVI** similar to the procedure for **LIII** (Step2 to Step 5)

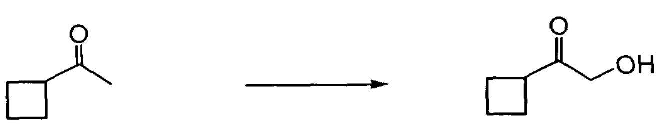
A number of inhibitors described in **table-6** using the intermediates **LVI** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LVII Preparation of intermediate of Formula LVII



LVII

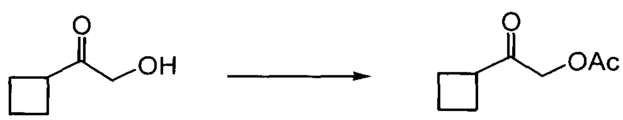
Step 1



LVIIa **LVIIb**

To the stirred solution of TFA (22.6 mL, 305 mmol), water (120 mL) and [bis(trifluoroacetoxy)iodo]benzene (131 g, 305 mmol) in acetonitrile (600 mL) was added cyclobutyl methyl ketone **LVIIa** (15.0 g, 153 mmol). The resulting solution was heated to reflux and stirred for 4 h. Acetonitrile was removed in vacuo. Water (120 mL) was added and the mixture was extracted with diethyl ether (2 X 500 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 30% Et_2O/hexane to give 8.82 g of **LVIIb** (51%).

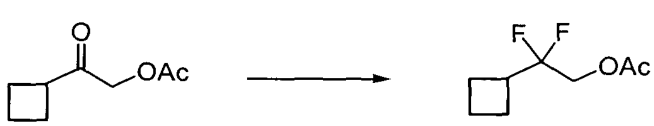
Step 2



LVIIb **LVIIc**

To the solution of **LVIIb** (1.4 g, 12.3 mmol), acetic anhydride (1.3 mL, 13.5 mmol) and triethyl amine (3.4 mL, 24.5 mmol) in CH_2Cl_2 (50 mL) was added DMAP (0.67 g, 5.5 mmol). The reaction mixture was stirred at rt for 4 h before 5% H_3PO_4 (50 mL) was added. After layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL). Combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo to 2.0 g crude product **LVIIc**.

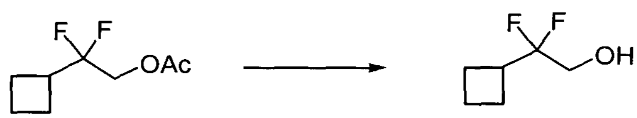
Step 3



LVIIc **LVIId**

The mixture of **LVIIc** (1.9 g, 12.2 mmol) and DAST (Diethyl amino sulfur trifluoride, 3.0 mL, 22.3 mmol) was heated to 50 C and stirred for 2 h. The mixturte was then slowly poured into ice water (50 mL), and extracted with diethyl ether (3 X 50 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 10-40% Et_2O/hexane to give 0.62 g of **LVIId** (29%) and 0.68 g starting material **LVIIc**.

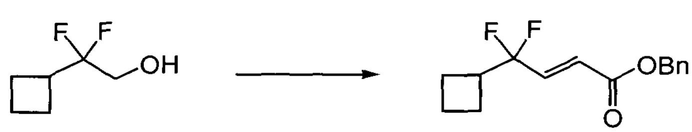
Step 4



LVIId **LVIIe**

The mixture of **LVIId** (3.10 g, 17.4 mmol) and lithium hydroxide (0.84 g, 34.8 mmol) in water (10 mL) was vigorously stirred at rt for 6 h before it was diluted with water (50 mL) and extracted with diethyl ether (3 X 60 mL). The combined organic solution was dried ($MgSO_4$), filtered and carefully concentrated in vacuo to give **LVIIe** 2.68 g crude product.

Step 5

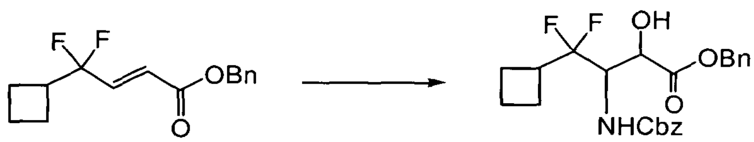


LVIIe **LVIIf**

The solution of compound **LVIIe** and Dess-Martin reagent in CH_2Cl_2 was stirred at rt for 1 h before $Ph_3P{=}CHCO_2Bn$ was added and stirring was continued for another 20 h. Diethyl ether was added followed by saturated NaS2O3 and saturated NaHCO3 solutions. After stirred for 15 min, the layers were separated. The organic solution was washed with saturated NaHCO3 and brine, dried

($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography to give the desired product **LVIIf**.

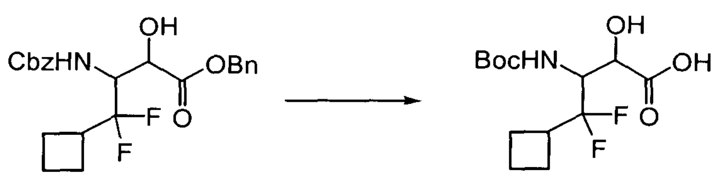
Step 6



LVIIf LVIIg

Compound **LVIIg** was prepared as described above (Step 4, Example **XXXXIII**) with appropriate amounts of reagents.

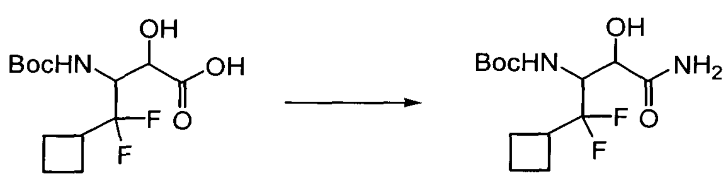
Step 7



LVIIg LVIIh

Catalytic hydrogenation of **LVIIg** over 10%Pd/C in MeOH followed by treatment with Boc_2O in $NaHCO_3$/THF/water will afford **LVIIh**.

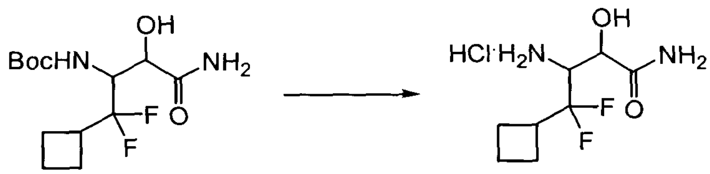
Step 8



LVIIh LVIIi

Conversion of **LVIIh** to compound **LVIIi** will follow previously described procedures (Step 5, Example **XXVIII**).

Step 9

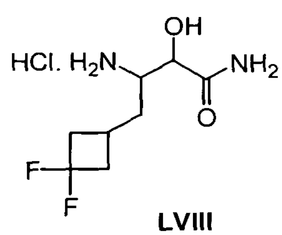


LVIIi **LVII**

Conversion of **LVIIi** to compound **LVII** follows previously described procedures (Step 9, Example **XXIII**).

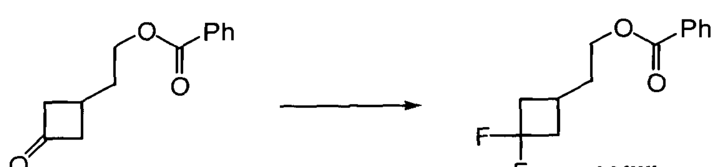
A number of inhibitors described in **table-6** using the intermediates **LVII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

<u>Example LVIII Preparation of intermediate of Formula LVIII</u>



LVIII

Step 1

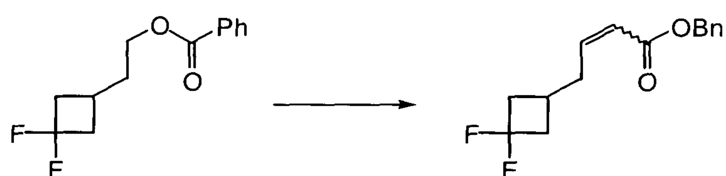


LVIIIa **LVIIIb**

To a solution of compound **LVIIIa** [for preparation of **LVIIIa** see J. Ramnauth and E. Lee-Ruff, *Can. J. Chem.*, **2001**, *79*, 114-120] (3g) in dichloromethane (75 mL)

was added DAST (Diethyl amino sulfur trifluoride, 9.1 mL) slowly and the reaction was stirred at room temperature overnight. The mixturte was slowly poured into ice/saturated sodium bicarbonate solution (100/200 mL) with stirring. Added 200 mL of dichloromethane and the organic layer was separated and washed with cold saturated sodium bicarbonate solution, brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography (5/95 EtOAc/hexanes) afforded 2.59 g of **LVIIIb**.

Step 2



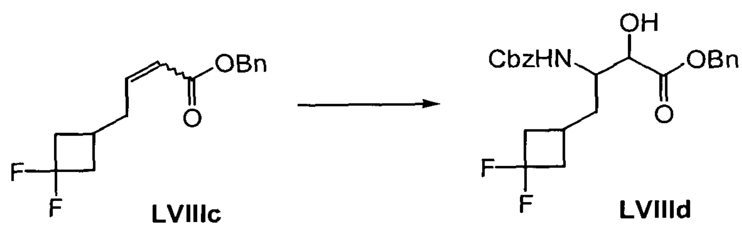
LVIIIb **LVIIIc**

Compound **LVIIIb** (3.42 g) was dissolved in THF/MeOH (1/1, 50 mL). To this was added a solution of potassium carbonate (1.97 g) in water (25 mL). The reaction mixture was stirred at room temperature for 4 hrs and then stored in the freezer (-10°C) overnight. The reaction mixture was warmed to room temperature over 3 hrs when TLC indicated complete consumption of **LVIIIb**. Brine (100 mL) was added to the reaction mixture and was extracted with ethyl ether (3 x 100 mL). The ether layers were combined, dried (Na_2SO_4) and concentrated to afford a residue (2.77g) which was processed further without purification.

The residue thus obtained was dissolved in CH_2Cl_2/DMSO (6/1, 140 mL). To this solution was added benzyl (triphenylphosphoranylidene)acetate (11.7 g) and then Dess-Martin's Periodinane (12.09 g, in three equal portions) carefully. The reaction mixture was stirred at room temperature for 4 hrs and quenched with cold sodium bicarbonate solution (200 mL) and diluted with CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was separated and washed with 10% $Na_2S_2O_3$ solution (125 mL), $NaHCO_3$ solution (125 mL), water (125 mL), dried (Na_2SO_4) and concentrated.

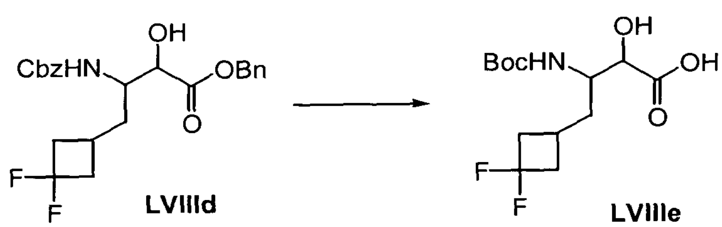
The residue was purified by column chromatography using 50/50 CH_2Cl_2/hexanes to afford the required compound, **LVIIIc** (2.25 g).

Step 3



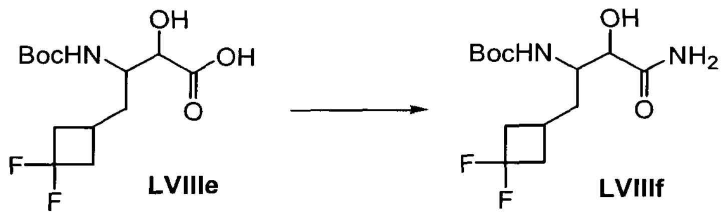
Compound **LVIIId** was prepared as described above (Step 4, Example **XXXXIII**) with appropriate amounts of reagents.

Step 4



Catalytic hydrogenation of **LVIIId** over 10%Pd/C in MeOH followed by treatment with Boc_2O in $NaHCO_3$/THF/water will afford **LVIIIe**.

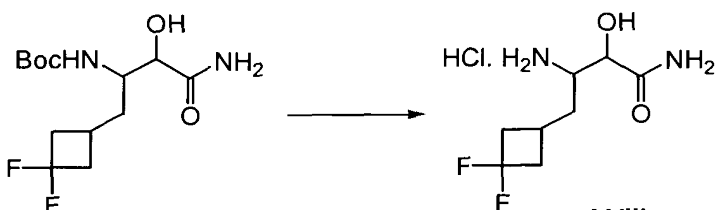
Step 5



LVIIIe LVIIIf

Conversion of **LVIIIe** to compound **LVIIIf** will follow previously described procedures (Step 5, Example **XXVIII**).

Step 6

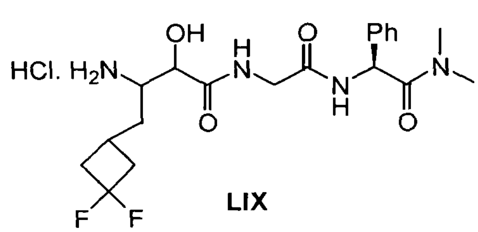


LVIIIf LVIII

Conversion of **LVIIIF** to compound **LVIII** will follow previously described procedures (Step 9, Example **XXIII**).

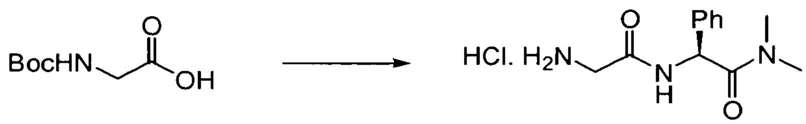
A number of inhibitors described in **table-6** using the intermediates **LVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LIX Preparation of intermediate of Formula LIX



LIX

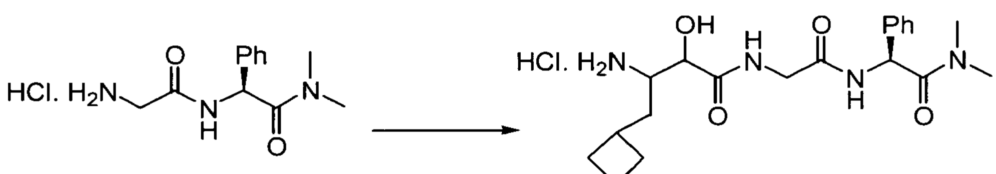
Step 1



LIXa **LIXb**

Commercially available N-Boc protected glycine **LIXa** was reacted with the amine **XV** from Example **XV** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LIXb**.

Step 2

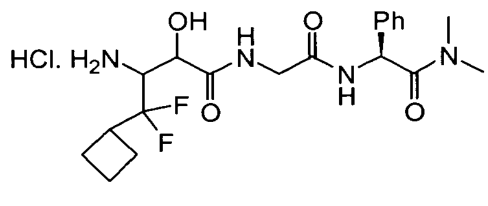


LIXb **LIX**

Acid **LVIIIe** (from above) can be reacted with **LIXb** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate can then be treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LIX**.

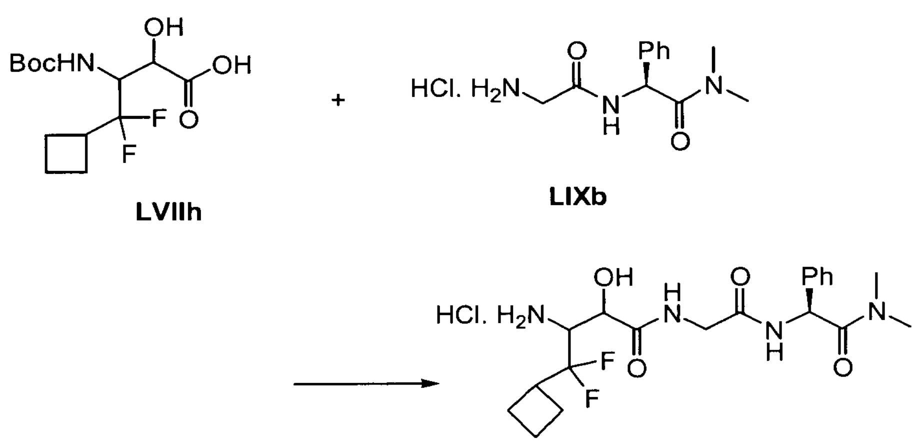
A number of inhibitors described in **table-6** using the intermediates **LIX** were synthesized following the procedures outlined for preparative **examples XXIX,** and **XXXX**

Example LX Preparation of intermediate of Formula LX



LX

Step 1

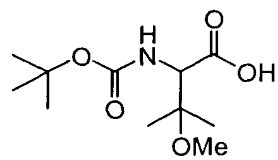


LVIIh **LIXb** **LX**

Acid **LVIIh** (from above) was reacted with **LIXb** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LX**.

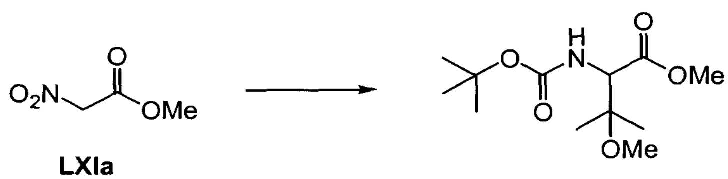
A number of inhibitors described in **table-6** using the intermediates **LIX** were synthesized following the procedures outlined for preparative **examples XXIX,** and **XXXX**

Example LXI Preparation of intermediate of Formula LXI



LXI

Step 1

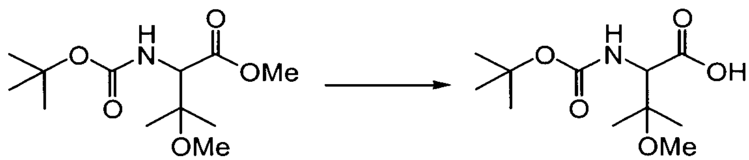


LXIa **LXIb**

To a solution of methyl nitroacetate **LXIa** (3 g) in benzene (15 mL) was added dimethoxy propane (6.2 mL) and acetic anhydride (4.87 mL). The mixture was refluxed overnight. The reaction mixture was concentrated. It was resubjected to the above conditions. The residue after concentration was taken in EtOAc (100 mL) and washed with cold saturated sodium bicarbonate solution (3 x 75 mL), brine (100 mL), dried (Na_2SO_4) and concentrated.

The residue from above was taken in MeOH (150 mL). Boc_2O (6 g) and 10% Pd/C (150 mg) were added and the mixture was hydrogenated using a balloon filled with hydrogen gas. After 24 hours, added some more 10% Pd/C and repeated the procedure. The reaction mixture was then filtered through celite, concentrated, and purified by column chromatography using 5/95 to 10/90 EtOAc/hexanes to afford 2.2 g of **LXIb**.

Step 2

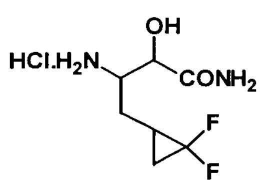


LXIb LXI

Compound **LXIb** was prepared from **LXI** in quantitative yield using procedures described above for the conversion of **XXVIg** to **XXVIh** (see Example **XXVI**).

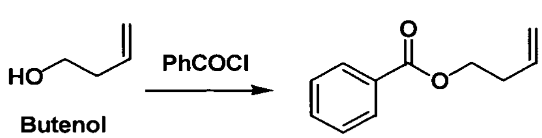
A number of inhibitors described in **table-6** using the intermediates **LVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LXII Preparation of intermediate of Formula LXII



LXII

Step1:

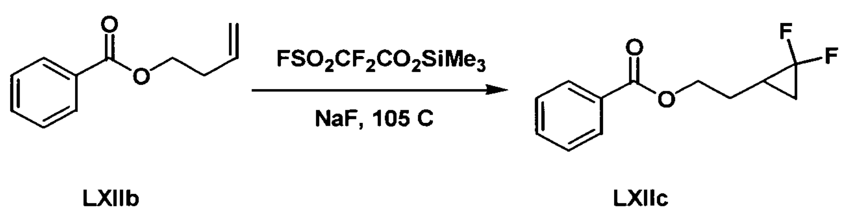


Butenol

LXIIa LXIIb

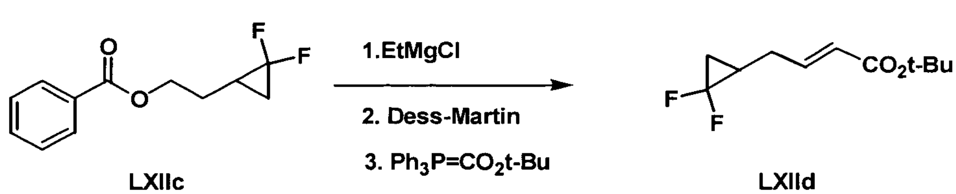
Butenol **LXIIa** was reacted in the manner previously described in preparative example XXXXIII step 1 to afford product **LXIIb**

Step2:



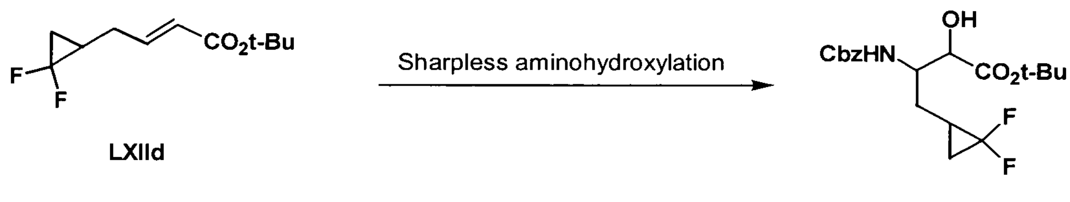
To 5.3g (30 mmol) of **LXIIb** product of step 1 was added 25 mg of NaF. At 110 °C, was added via syringe-pump 1.6equiv (48 mmol, 12g) of TMSfluorosulfonyldifluoroacetate (TFDA) in 2h. After 2h, reaction is cooled down to RT. Purification by flash column chromatography (3% EtOAc, Hexane, silica) furnished **LXIIc**, Product of step 2 (4.93g).

Step3:



Product of step 2, **LXIIc** (1g) was treated in the manner previously described in step3 of preparative **XXXXIII** to afford **LXIId,** Product of step 3 (0.89g)

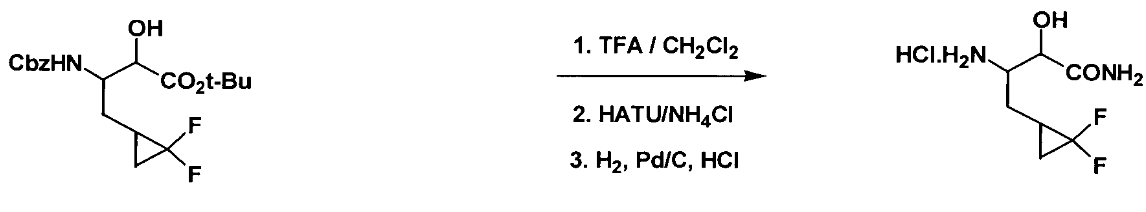
Step4:



LXIId LXIIe

Product of step 3, **LXIId** (3.2g) was treated in the manner previously described in step4 of preparative **XXXXIII** to afford Product **LXIIe** (1.4g).

Step5:

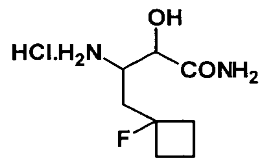


LXIIe LXIIf

Product of step 4, **LXIIe** (0.54g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXIIf** (0.24g).

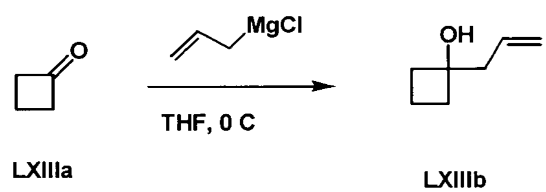
A number of inhibitors described in **table-6** using the intermediate **LXII** were synthesized following the procedures outlined for preparative examples **XXIII**, **XXIV**, **XXVIII**, **XXIX**, and **XXXX**

<u>Example LXIII Preparation of intermediate of Formula LXIII</u>



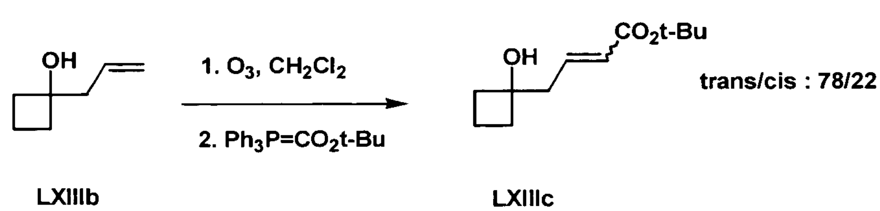
LXIII

Step1:



To a –78 °C solution of cyclobutanone (15g, 214 mmol) in THF (100 mL) is added dropwise Allylmagnesiumchloride (2.0 M in THF, 1.1 equiv, 118 mL). After 1 hour, reaction is stopped by the addition of ice and HCl 1.0 N (100 mL). The mixture was diluted with ethyl acetate (~200 ml) and the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuo and purification by chromatography over silica gel (10% ethyl acetate in n-hexane) provided product **LXIIIb** (21g).

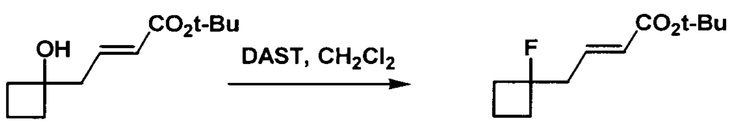
Step2:



To a –78 °C solution of product of step 1, **LXIIIb** (11.2g) in CH_2Cl_2 (200 mL) is bubbled Ozone until a persistent blue color was observed (after 1 hour). Ozone was stopped and N_2 was flushed into the reaction mixture for 10 minutes. Me_2S (10 equiv., 7.3 mL) was added and reation was gradually warmed-up to room temperature overnight.

After 18 hours, $Ph_3P{=}CHCOO^tBu$ (40 g) was added. Stirring was continued for ~24 hrs Evaporation under vacuum provided the crude product which was chromatographed over silica gel (10% ethyl acetate in n-hexane) to provide product **LXIIIc** as a mixture of isomers (6.65g of trans isomer) and (1.9g of cis olefin).

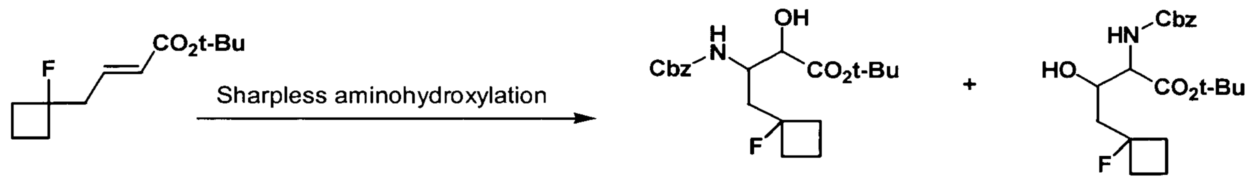
Step3:



LXIIIc LXIIId

To a 0 °C solution of product of step2, **LXIIIc** (0.21g) in CH_2Cl_2 (3 mL) is added DAST (1.1 equiv., 0.135 mL). After 15 minutes, reaction was stopped by the addition a cold saturated solution of Na_2CO_3 (150 ml). The mixture was diluted with ethyl acetate (~10 ml) and after stirring for ~30 min the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuum and purification by chromatography over silica gel (5% to 10% CH_2Cl_2 in n-hexane) provided **LXIIId** (0.1 g; 47%).

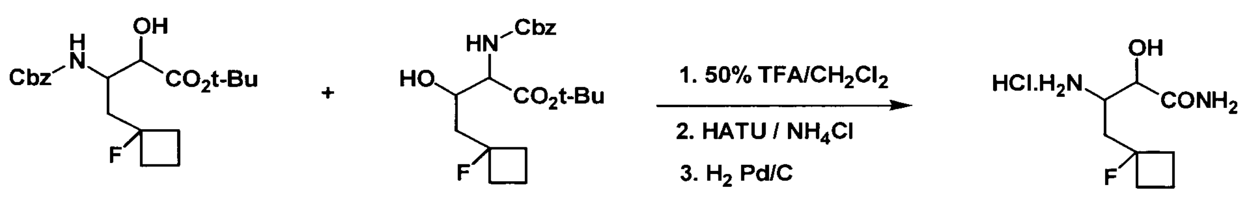
Step4:



LXIIId LXIIIe LXIIIf

Product of step 3, **LXIIId** (3.5g) was treated in the manner previously described in step4 of preparative **XXXXIII** to afford Products **LXIIIe and LXIIIf** as a mixture (3.25g).

Step5:

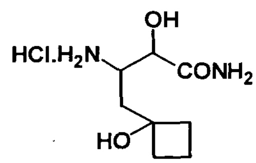


LXIIIe LXIIIf LXIII

Products of step 4 **(LXIIIe+LXIIIf)** (2.3g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXIII** (0.47g).

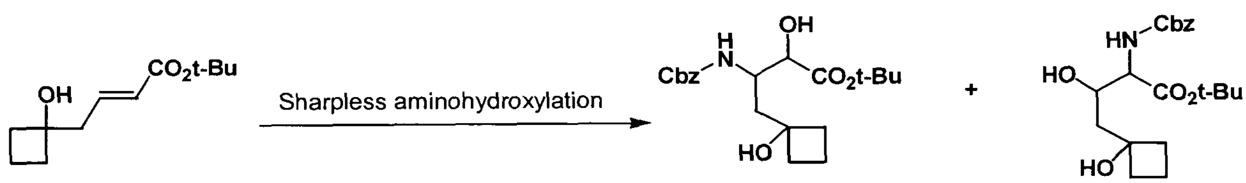
A number of inhibitors described in **table-6** using the intermediate LXII were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX**, and **XXXX**

<u>Exampl LXIV Preparation of intermediate of Formula LXIV</u>



LXIV

Step1:



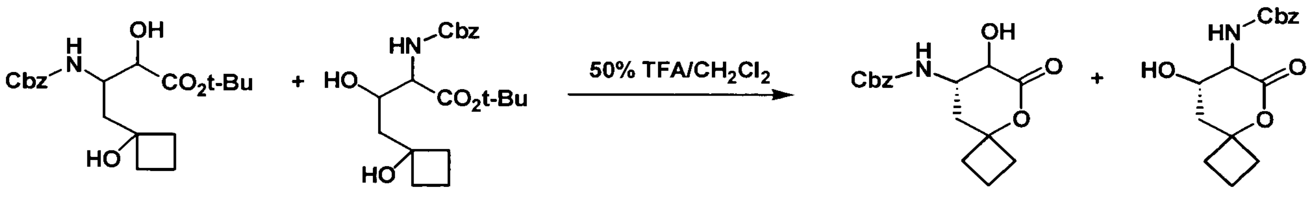
LXIIIc
"trans isomer'

LXIVa

LXIVb

Product **LXIIIc** (1.36g) was treated in the manner previously described in step4 of preparative example **XXXXIII** to afford Products **LXIVa** and **LXIVb** as a mixture (1.3g).

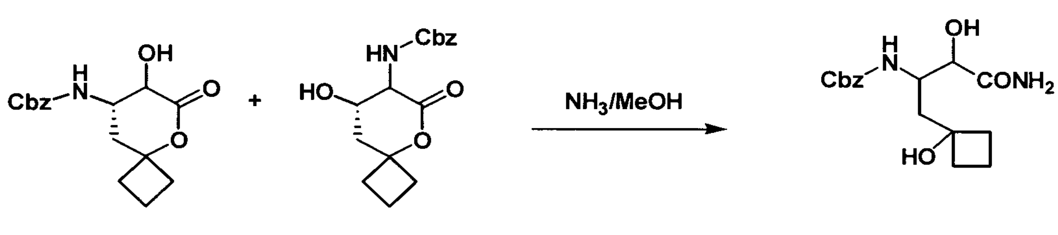
Step2:



LXIVa LXIVb LXIVc LXIVd

A stirred solution of Products of step 1 (**LXIVa+LXIVb**) (1.2g) in CH_2Cl_2 (40 ml) was treated with trifluoroacetic acid (40 ml). After 45 minutes the reaction mixture was concentrated to dryness under vacuum. The residue was chromatographed over silica gel (2% MeOH in CH_2Cl_2) to provide products **LXIVc** and **LXIVd** as a mixture (0.97g).

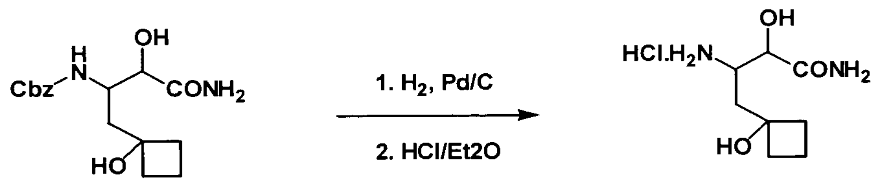
<u>Step3:</u>



LXIVc LXIVd LXIVe

To products of step 2 (**LXIVc+LXIVd**) (0.4g) was added 30 mL of NH_3 (2.0 M in MeOH). After 4 hours, the reaction mixture was concentrated to dryness under vacuum. The residue was preparative chromatography over silica gel (100% CH_3CN) to provide desired product **LXIVe** (0.3g).

<u>Step4:</u>

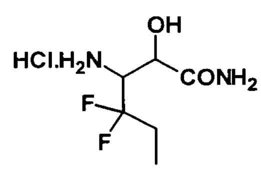


LXIVe LXIV

Product of step 3 **LXIVe** (0.054g) was treated in the manner previously described in step7 of preparative example XXXXIII to afford Product **LXIV** (0.032g)

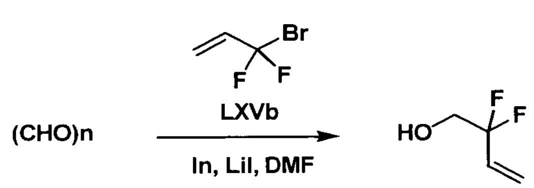
A number of inhibitors described in **table-6** using the intermediate **LXII** were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX**, and **XXXX**

Example LXV Preparation of intermediate of Formula LXV



LXV

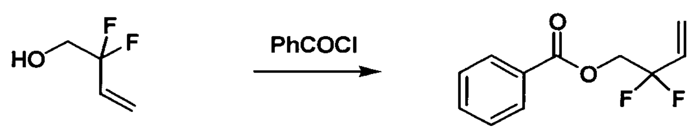
Step1:



LXVa LXVc

To a room temperature solution of paraformaldehyde **LXVa** (12g, 400 mmol) and 1-bromo-1,1-difluorop2-ene **LXVb** (6.3g, 40 mmol) in DMF (100 mL) was added In(0) (6.5g, 57 mmol) and LiI (0.4g, 3 mmol). The resulting slurry was stirred at RTfor 48 h . After 48 h, reaction was filtered trough a pad of celite. The filtrate was diluted with EtOAc (250 mL) and washed with H_2O (3 times) then brine. The organic phase separated and finally dried over anhydrous $MgSO_4$. Evaporation under vacuum provided product **LXVc**, which was used as it is directly in the next step.

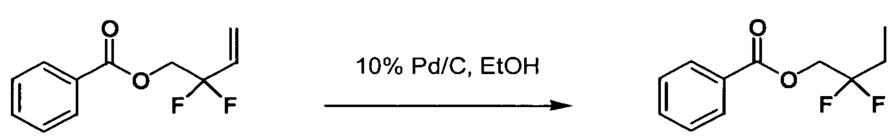
Step2:



LXVc LXVd

Product of step 1, **LXVc** (4g, 37 mmol) was reacted in the manner previously described in preparative example **XXXXIII step 1** to afford after purification by chromatography over silica gel (10% to 50% CH_2Cl_2 in n-hexane) product **LXVd** (4.3g).

Step3:

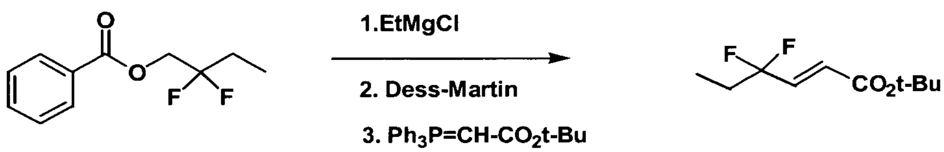


LXVd LXVe

To a solution of the product from step 2, **LXVd** (3.8 g) in ethanol (30 ml) was added 10% Pd/C catalyst (0.76g). The resulting suspension was hydrogenated until NMR experiment indicated complete consumption of the starting material (~4

hrs). The catalyst was removed by filtration trough a pad of celite and washed with ethanol. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product, **LXVe** (3.8g).

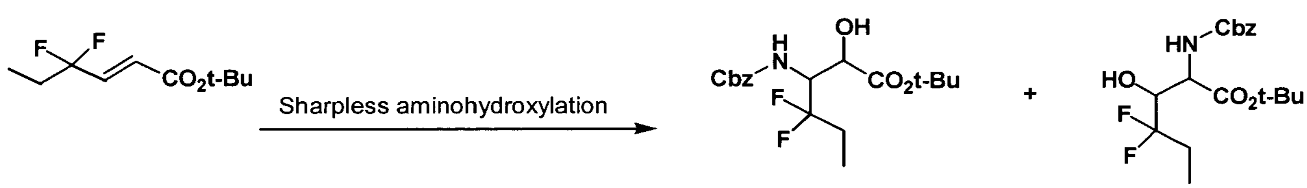
Step4:



LXVe LXVf

Product of step 3, **LXVe** (3.4g) was treated in the manner previously described in step3 of **XXXXIII** to afford Product **LXVf** (2.5g).

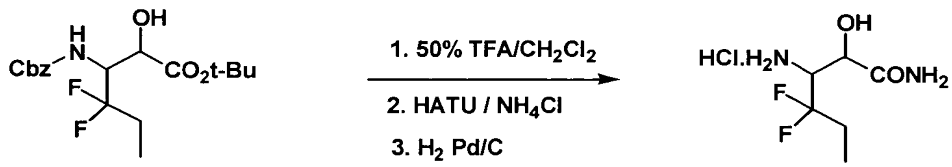
Step5:



LXVf LXVg LXVh

Product of step 4, **LXVf** (2g) was treated in the manner previously described in step4 of preparative example **XXXXIII** to afford after purification by chromatography over silica gel (30% EtOAc in n-hexane) to give **LXVg** (0.27g) and **LXVh** (0.26g).

Step6:



LXVg LXV

Product of step 5 **LXVg** (0.17g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXV** (0.025g).

A number of inhibitors described in **table-6** using the intermediate **LXV** were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX**, and **XXXX**

Seperation of diastereomers: The diastereomers arising from the α-center of ketoamide were seperated using either chromatography (SiO_2) or HPLC (YMC diol column) with Hexane/CH_2Cl_2/Isopropanol/CH_3CN = 85/7.5/6.5/1 as the solvent, as is known to those skilled in the art.

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or

chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

Materials: Chemical reagents for assay related buffers were obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framingham, Massachusetts). Peptides were synthesized manually or on an automated ABI model 431A synthesizer (from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block was from USA Scientific (Ocala, Florida) and the 96-well plate vortexer was from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer was obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) was prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations were determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) was exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 μM EDTA and 5 μM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates was done as reported by R. Zhang *et al*, (*ibid.*) and was initiated by anchoring Fmoc-Nva-OH to

2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides were subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments were cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash was evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase was dried over Na_2SO_4 and evaporated.

The ester substrates were assembled using standard acid-alcohol coupling procedures (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments were dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) was added to initiate the coupling reactions. Product formation was monitored by HPLC and found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent was evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester was deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate was purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification was approximately 20-30%. The molecular mass was confirmed by electrospray ionization mass spectroscopy. The substrates were stored in dry powder form under desiccation.

Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products were obtained in the pH 6.5 assay buffer. Extinction coefficients were determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple

dilutions. The optimal off-peak wavelength was defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

Protease Assay: HCV protease assays were performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al*, *ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO 4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl).The plates were monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) were calculated assuming the enzyme was fully active.

Evaluation of Inhibitors and Inactivators: The inhibition constants (Ki*) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive

inhibition kinetics: $v_o/v_i = 1 + [I]_o/(Ki^* (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(Ki^*(1+[S]_o/K_m)$, was used to calculate the Ki* value.

The obtained Ki* values for the various compounds of the present invention are given in the afore-mentioned Tables wherein the compounds have been arranged in the order of ranges of Ki* values. From these test results, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility as NS3-serine protease inhibitors.

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Table 2

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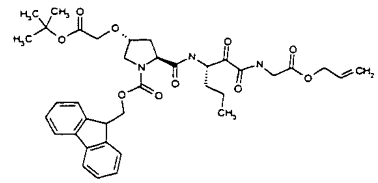
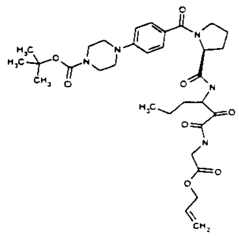
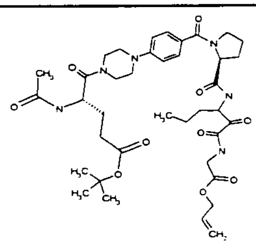
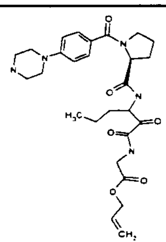
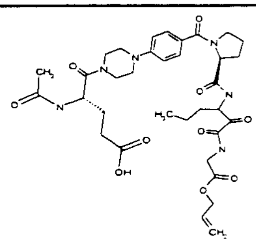
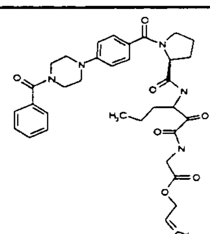
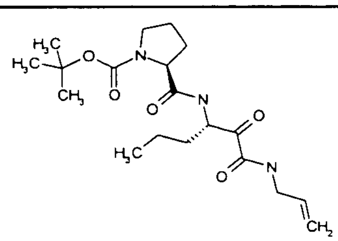
1		691.7853
2		627.7441
3		754.8883
4		527.6259
5		698.7799
6		631.7352
7		381.476

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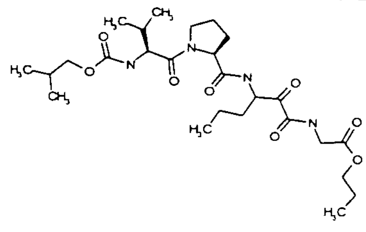
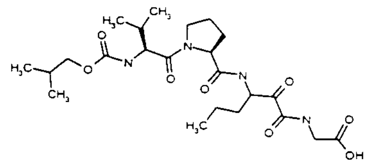
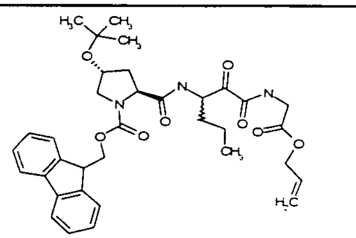
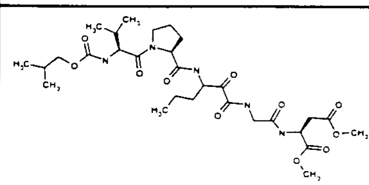
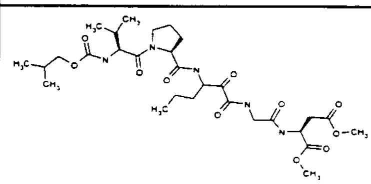
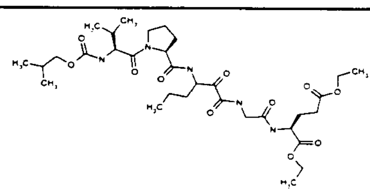
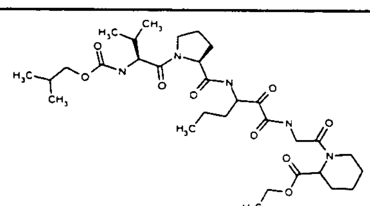
8		540.6626
9		498.5813
10		633.7482
11		641.7249
12		641.7249
13		683.8061
14		637.7802

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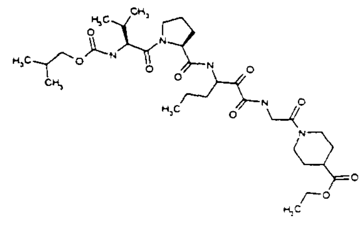
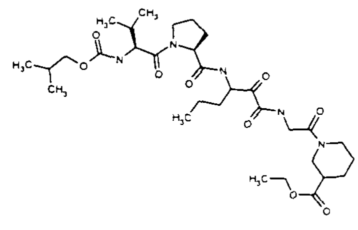
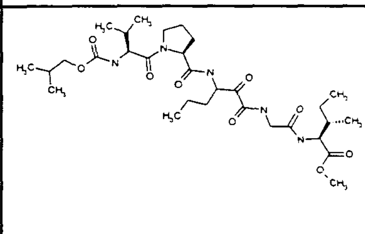
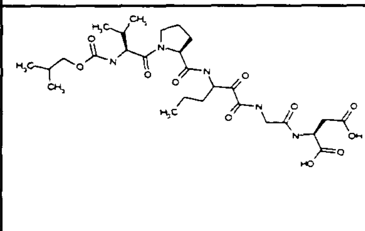
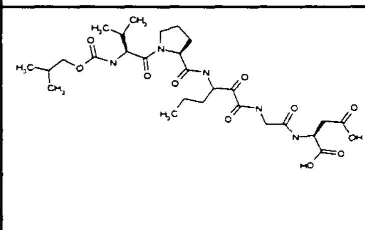
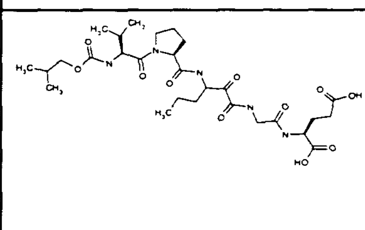
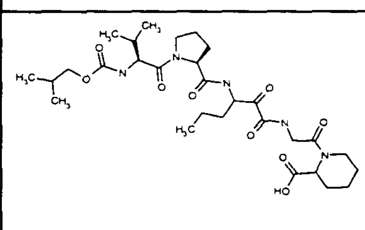
15		637.7802
16		637.7802
17		625.769
18		613.6707
19		613.6707
20		627.6978
21		609.726

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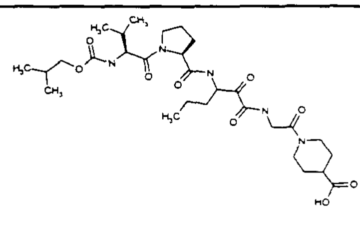
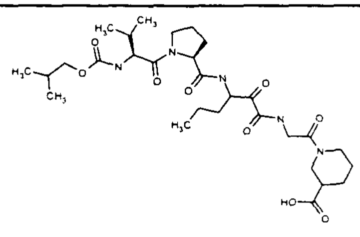
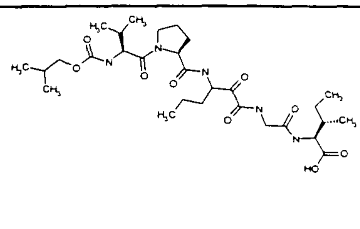
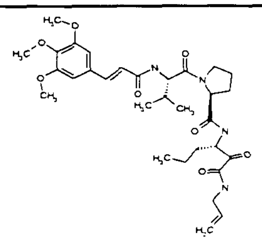
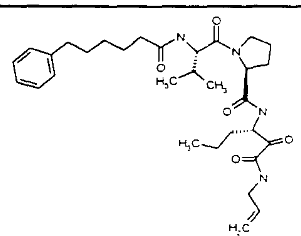
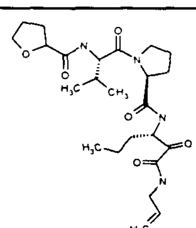
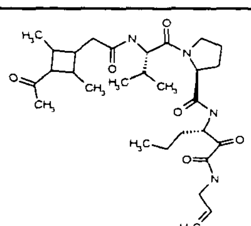
22		609.726
23		609.726
24		611.742
25		600.7183
26		554.7361
27		478.5937
28		546.7132

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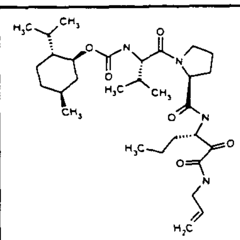
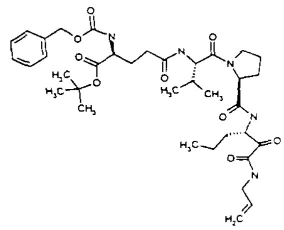
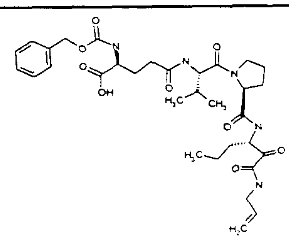
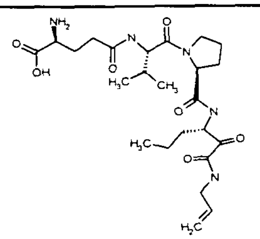
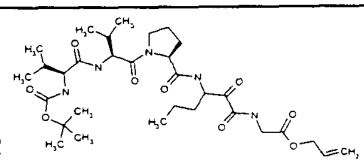
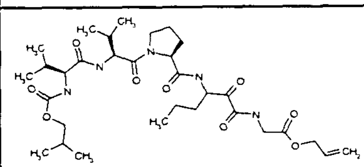
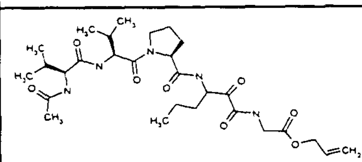
29		562.7562
30		699.8519
31		643.7435
32		509.6077
33		637.7802
34		637.7802
35		579.6995

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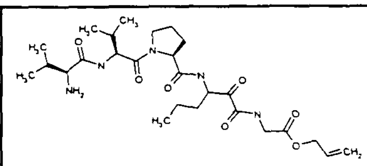
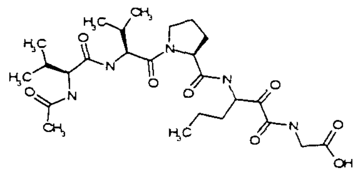
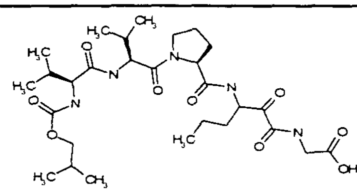
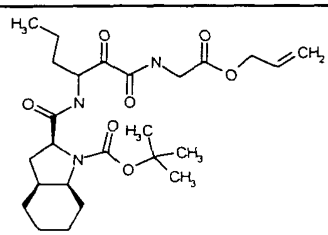
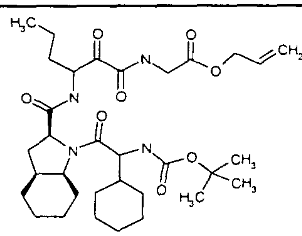
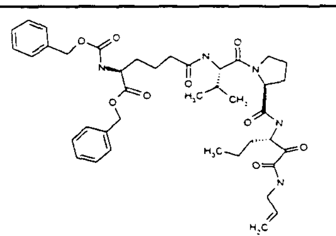
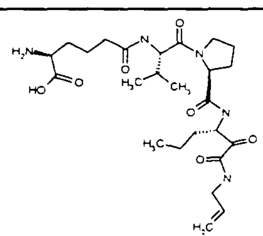
36		537.6619
37		539.6342
38		597.7149
39		493.6055
40		632.8044
41		747.8965
42		523.6348

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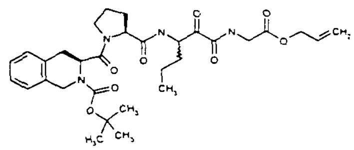
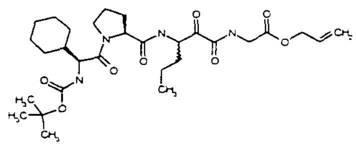
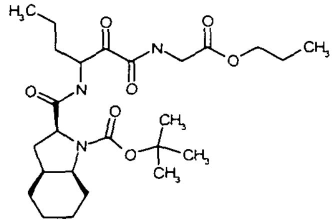
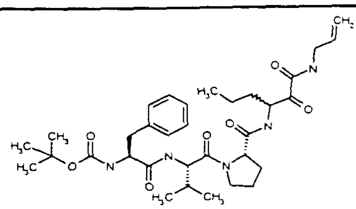
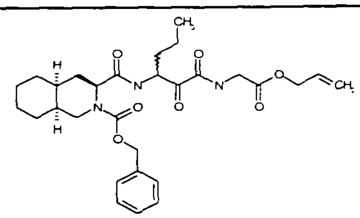
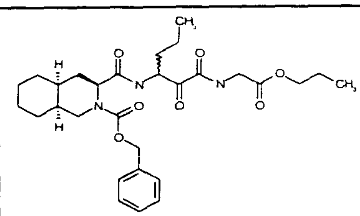
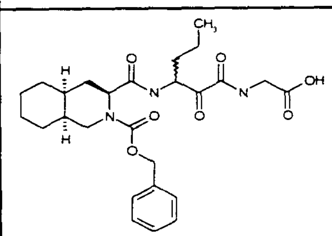
43		598.7024
44		578.712
45		495.6214
46		627.7878
47		541.6501
48		543.666
49		501.5847

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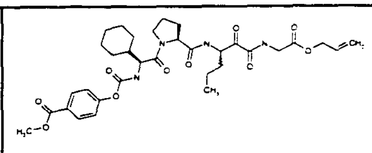
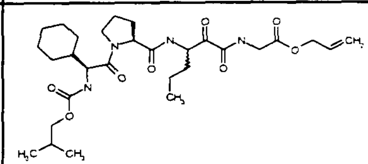
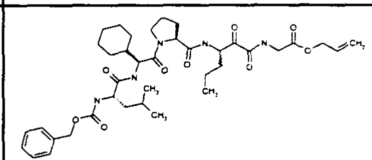
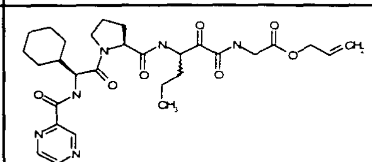
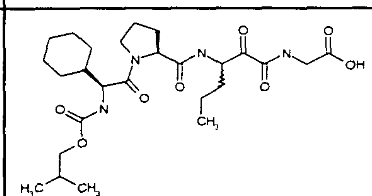
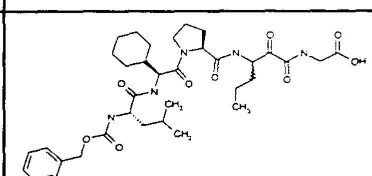
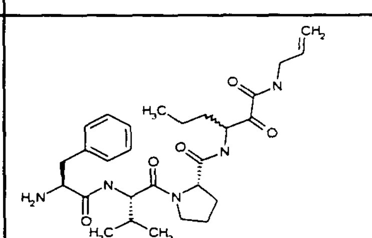
50		656.7394
51		578.712
52		725.8901
53		584.6782
54		538.6467
55		685.8248
56		527.6695

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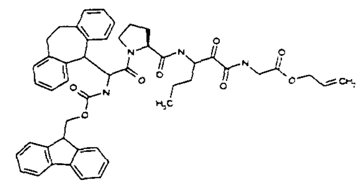
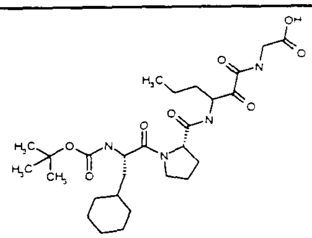
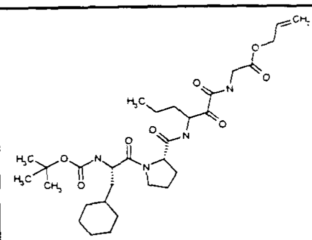
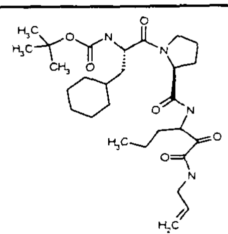
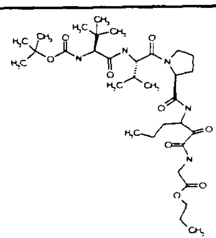
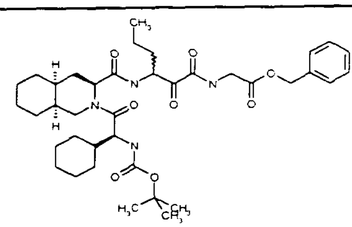
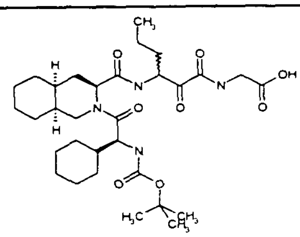
57		810.9557
58		552.6737
59		592.7391
60		534.702
61		653.8232
62		696.892
63		606.7662

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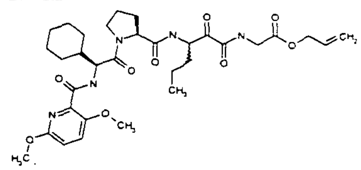
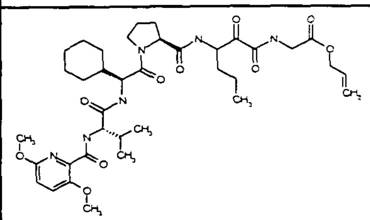
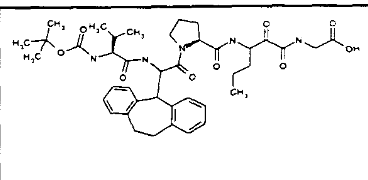
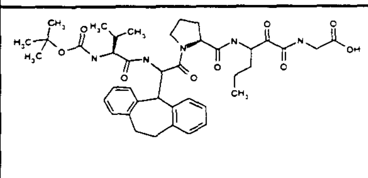
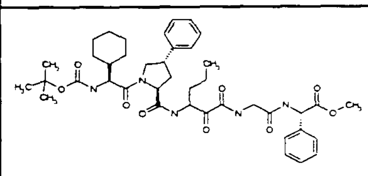
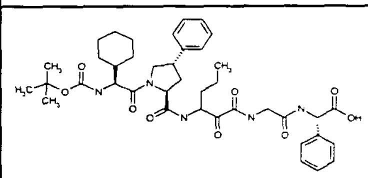
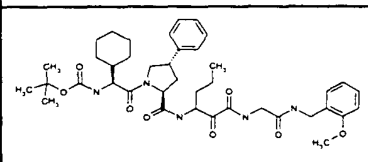
64		643.7435
65		742.8771
66		747.8965
67		747.8965
68		761.9236
69		747.8965
70		733.913

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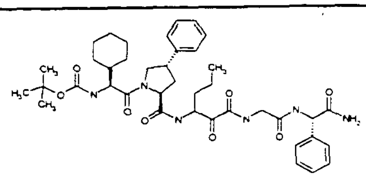
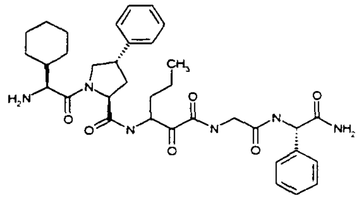
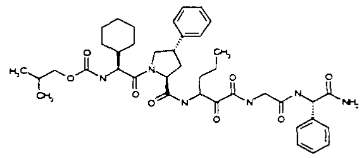
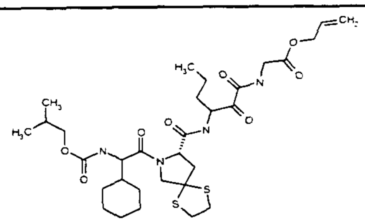
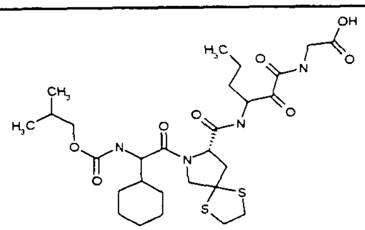
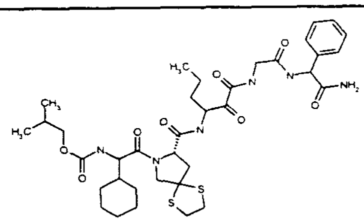
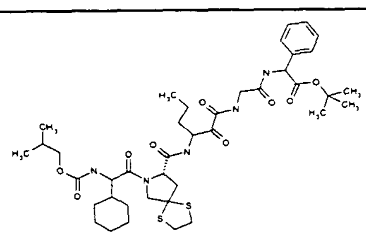
71		746.9118
72		646.7935
73		746.9118
74		668.8782
75		628.8129
76		760.9792
77		818.0723

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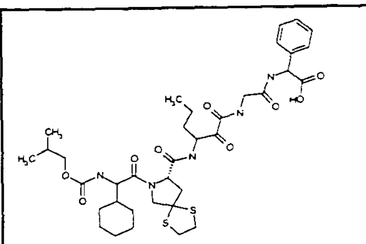
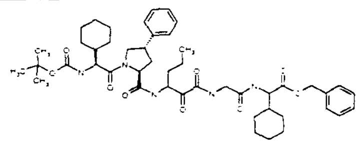
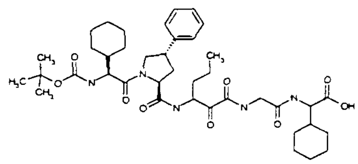
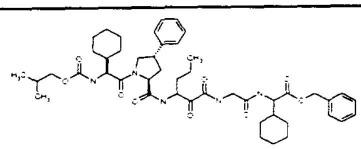
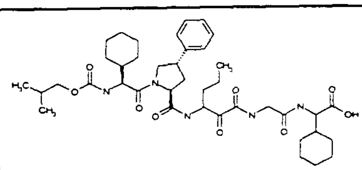
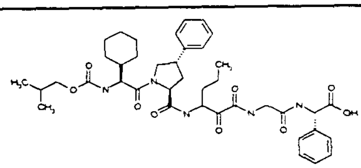
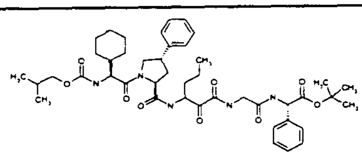
78		761.964
79		844.0702
80		753.9443
81		844.0702
82		753.9443
83		747.8965
84		804.0049

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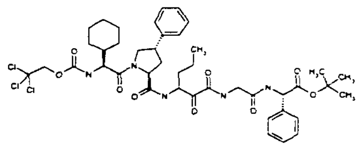
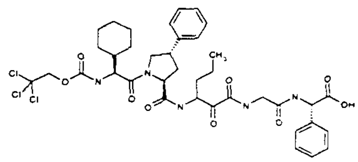
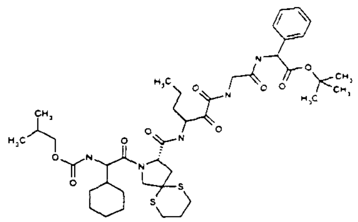
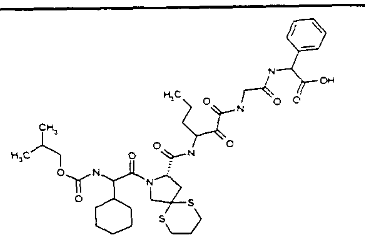
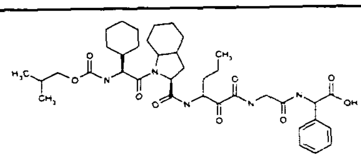
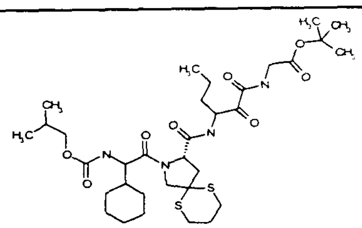
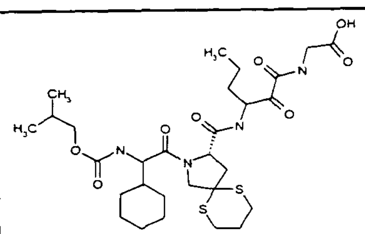
85		879.2858
86		823.1774
87		832.0994
88		775.9911
89		725.8901
90		698.9483
91		642.84

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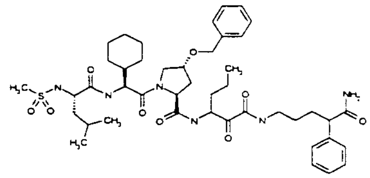
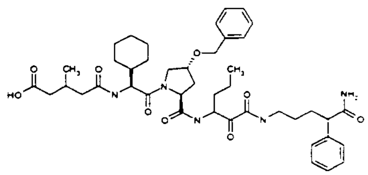
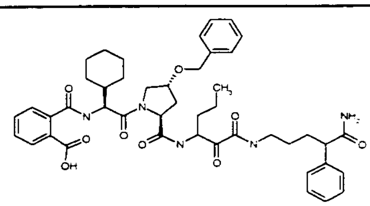
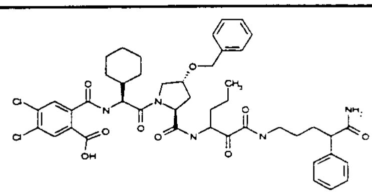
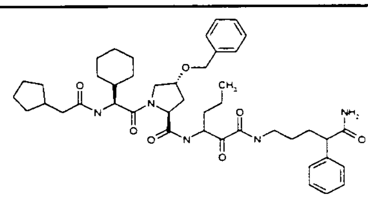
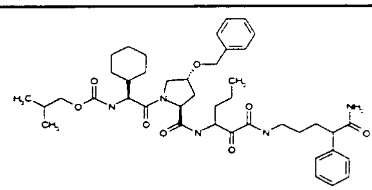
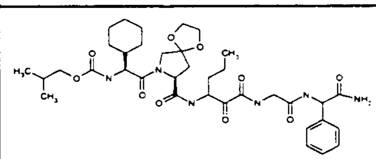
92		853.0995
93		789.9778
94		809.9682
95		878.8583
96		772.006
97		761.9672
98		728.85

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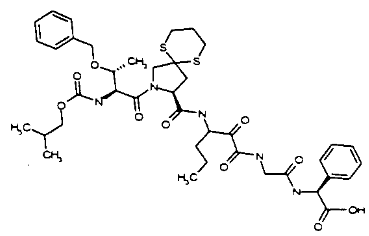
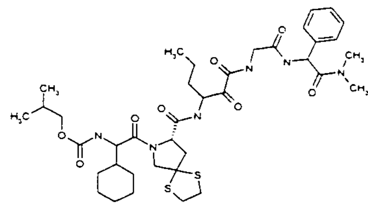
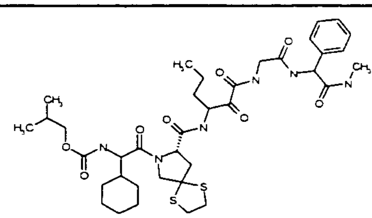
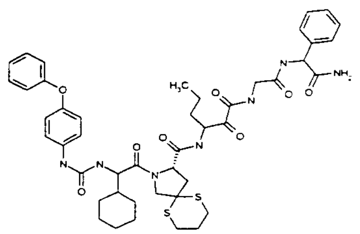
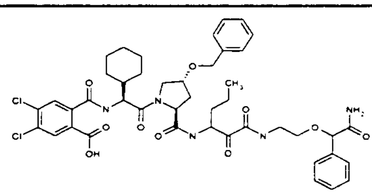
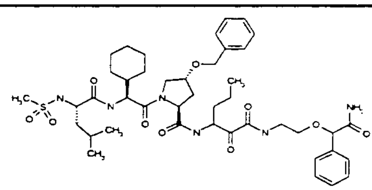
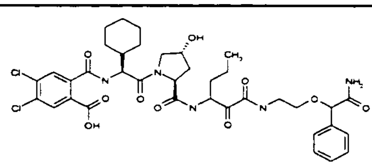
99		828.0239
100		789.0334
101		775.0063
102		886.1102
103		880.8306
104		855.0718
105		790.7047

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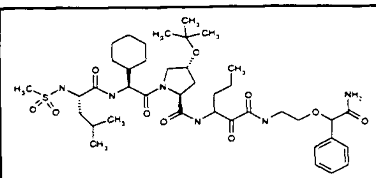
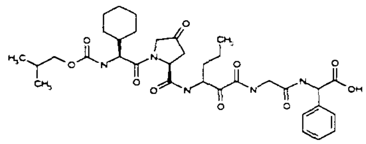
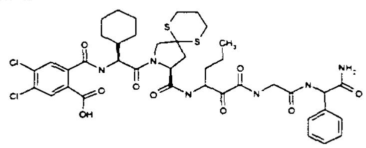
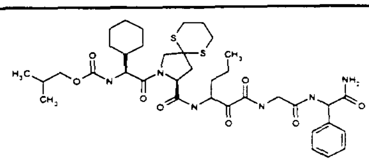
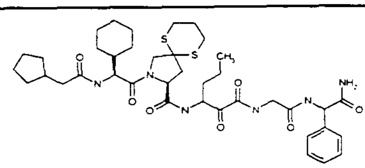
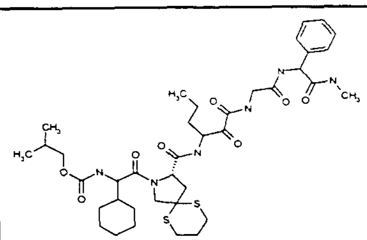
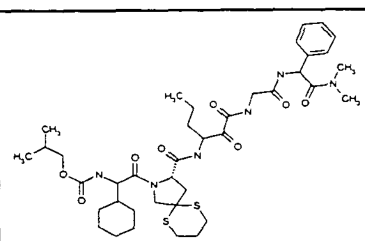
106		821.0543
107		685.7812
108		891.8973
109		775.0063
110		785.0452
111		789.0334
112		803.0605

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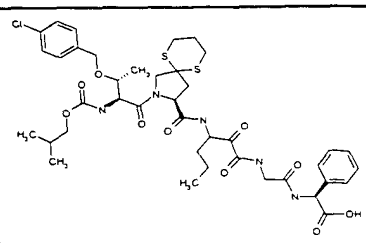
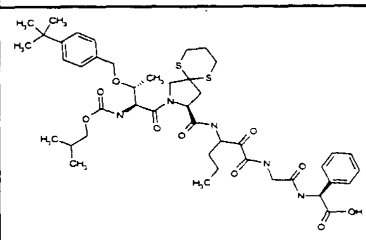
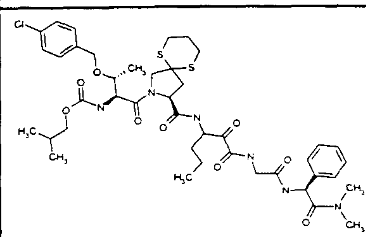
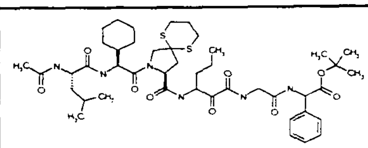
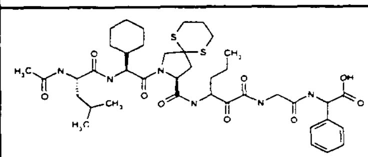
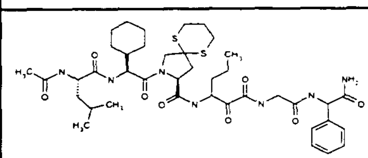
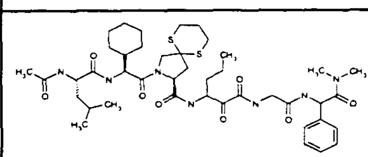
113		862.4689
114		884.1323
115		889.5384
116		887.1794
117		831.071
118		830.0863
119		858.1405

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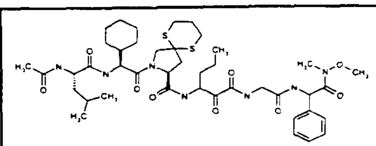
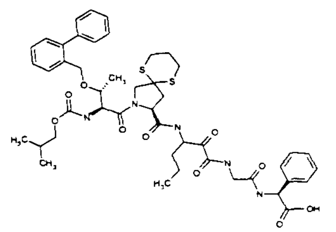
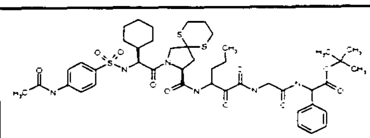
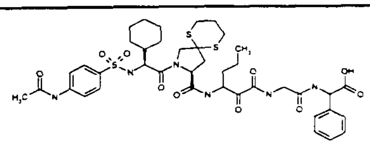
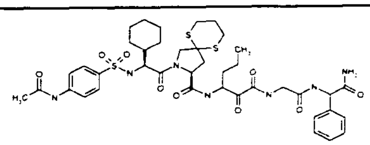
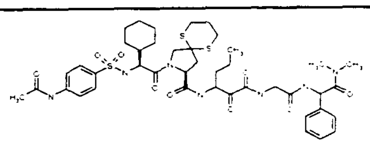
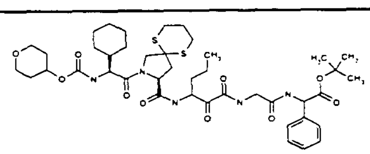
120		874.1399
121		904.1227
122		929.195
123		873.0867
124		872.1019
125		900.1561
126		860.11

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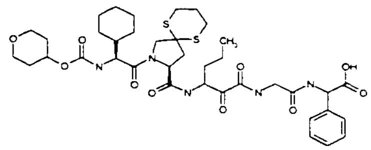
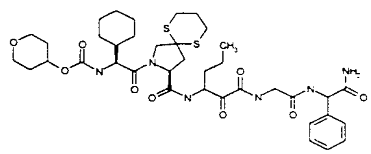
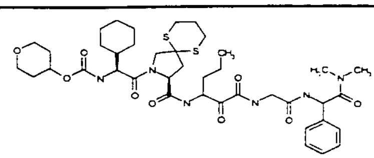
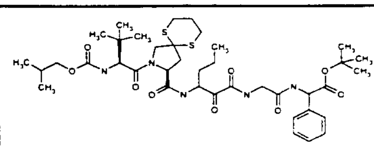
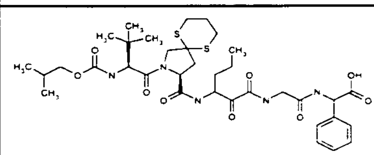
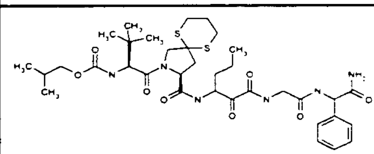
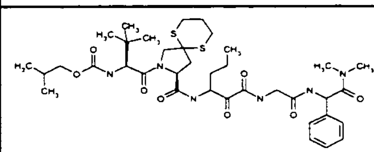
127		804.0016
128		803.0169
129		831.071
130		806.0612
131		749.9528
132		748.9681
133		777.0223

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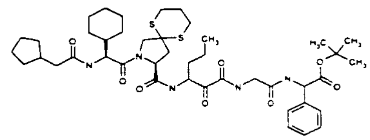
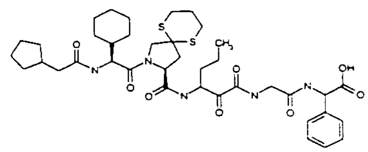
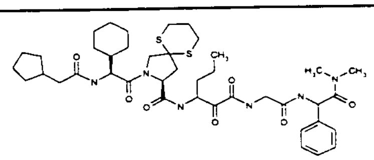
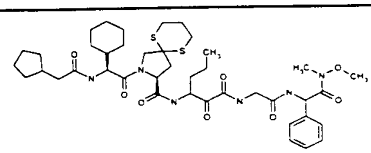
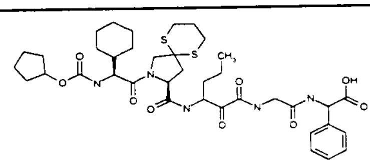
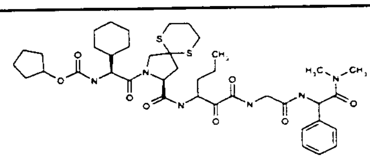
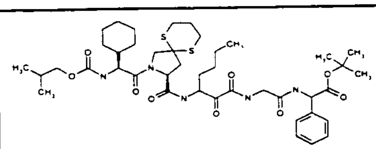
134		842.1382
135		786.0299
136		813.0994
137		829.0988
138		788.0022
139		815.0717
140		846.1265

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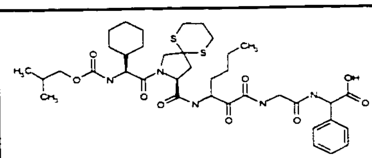
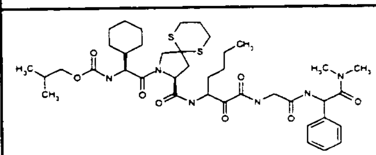
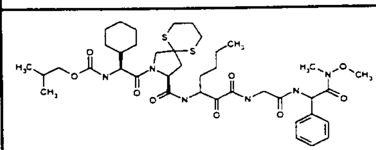
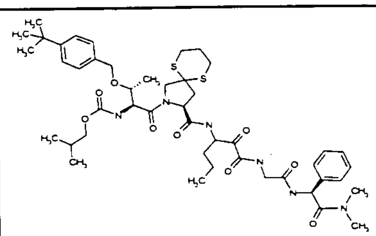
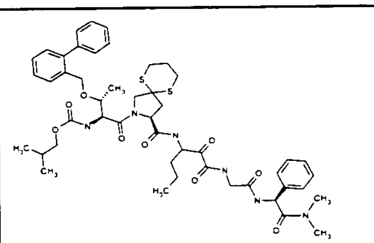
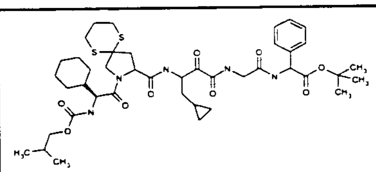
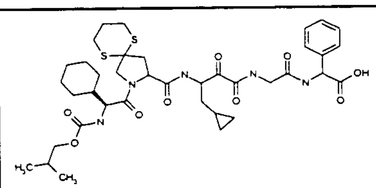
141		790.0181
142		817.0876
143		833.087
144		911.2017
145		931.1921
146		844.1106
147		788.0022

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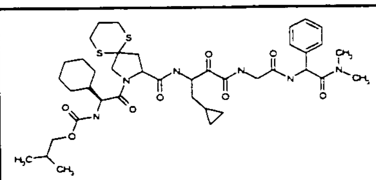
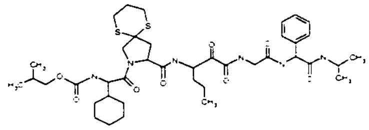
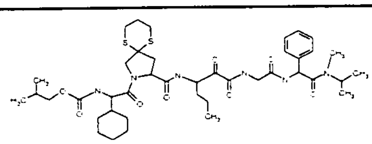
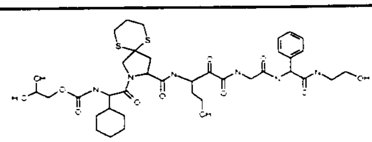
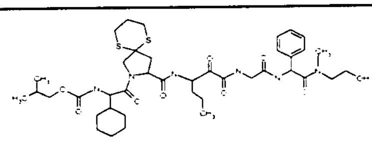
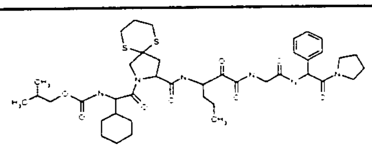
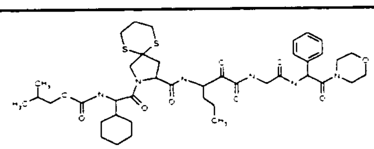
148		815.0717
149		817.0876
150		831.1147
151		819.0599
152		833.087
153		829.0988
154		845.0981

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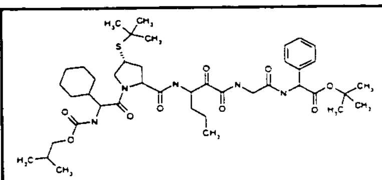
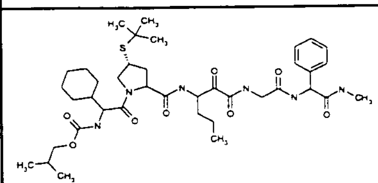
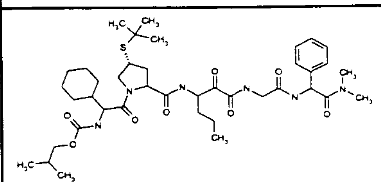
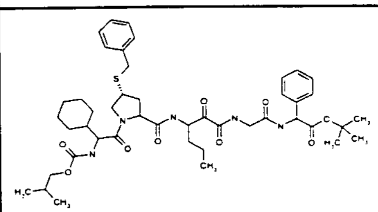
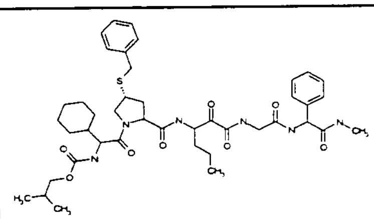
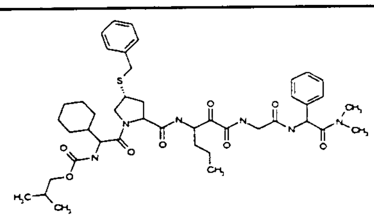
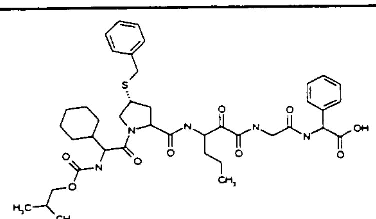
155		816.0784
156		773.0125
157		787.0396
158		850.0959
159		807.03
160		821.0571
161		793.9876

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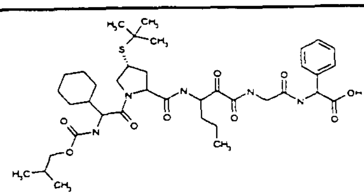
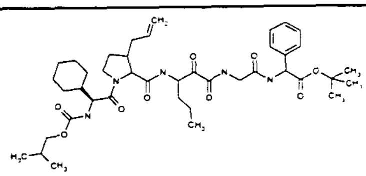
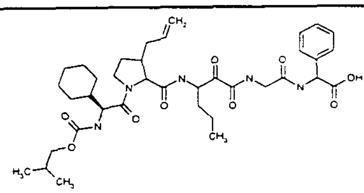
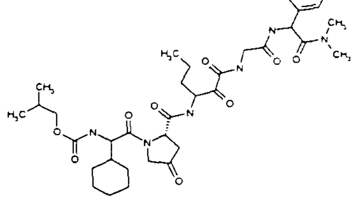
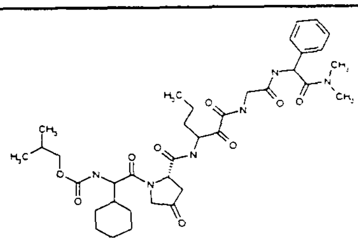
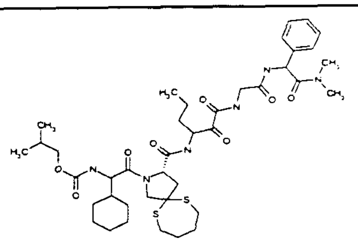
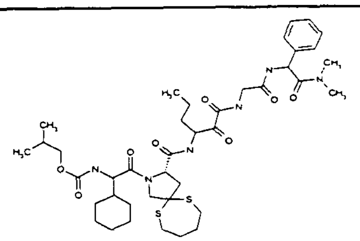
162		759.9701
163		767.9714
164		711.863
165		712.8506
166		712.8506
167		817.0876
168		817.0876

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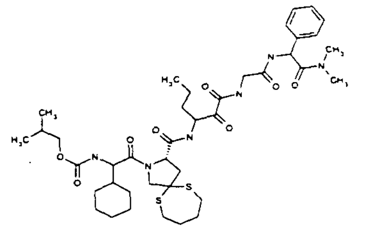
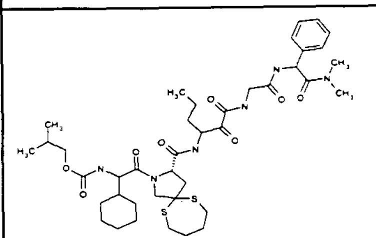
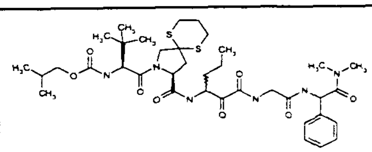
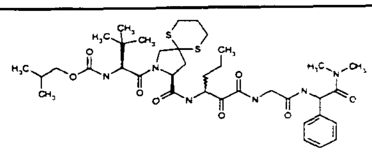
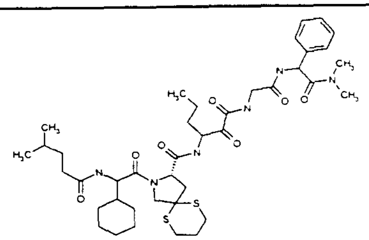
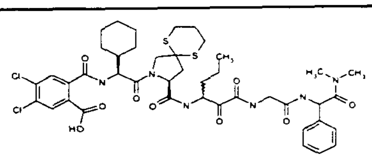
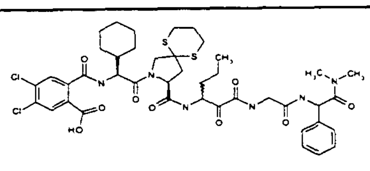
169		817.0876
170		817.0876
171		777.0223
172		777.0223
173		801.0882
174		919.9515
175		919.9515

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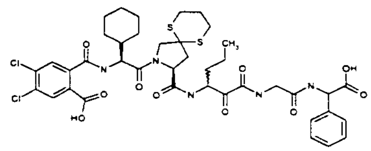
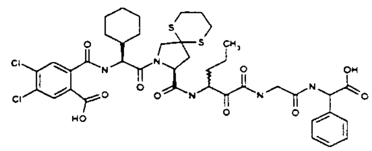
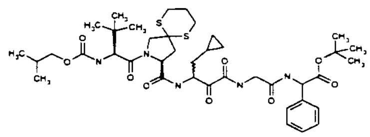
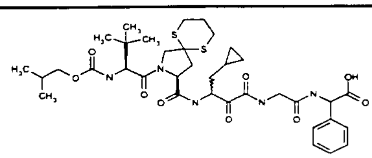
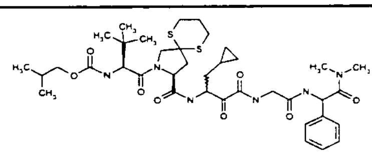
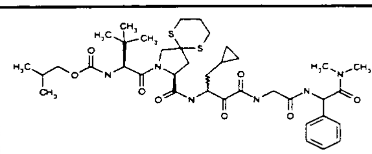
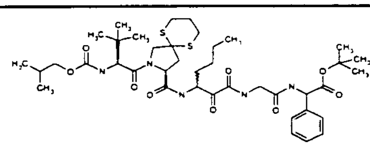
176		892.8821
177		892.8821
178		818.0723
179		761.964
180		789.0334
181		789.0334
182		820.0883

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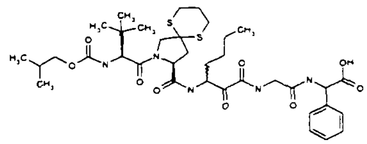
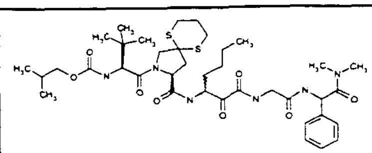
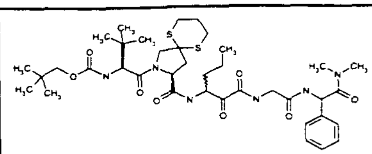
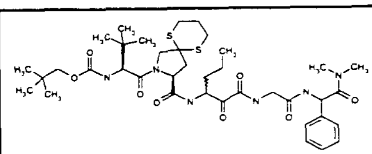
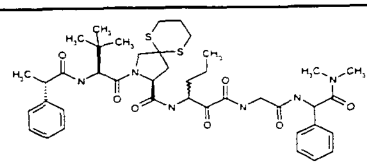
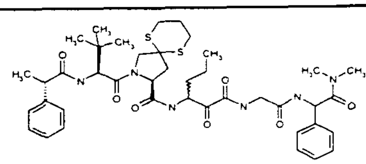
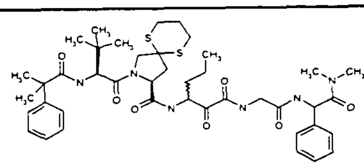
183		763.9799
184		791.0494
185		791.0494
186		791.0494
187		809.0674
188		809.0674
189		823.0945

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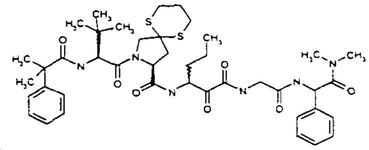
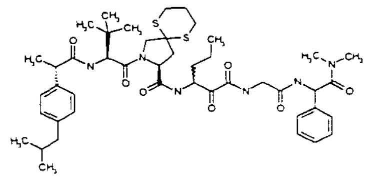
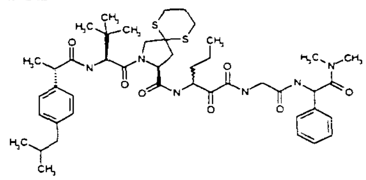
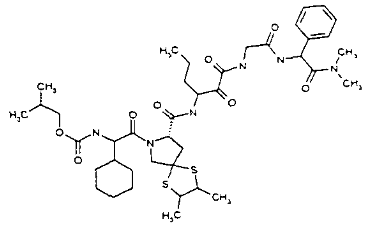
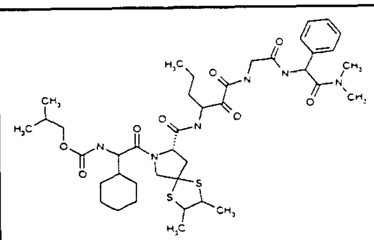
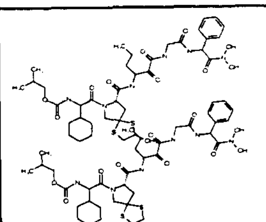
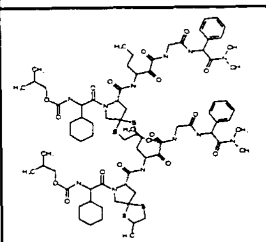
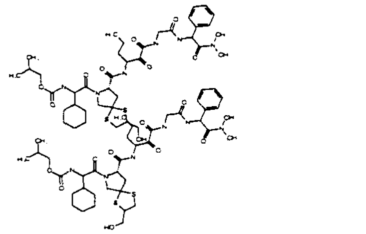
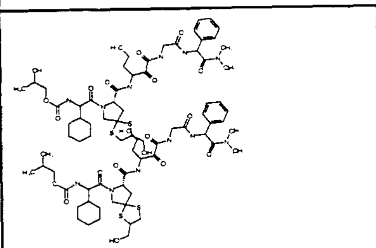
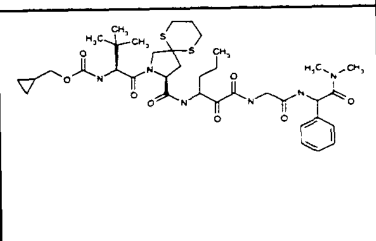
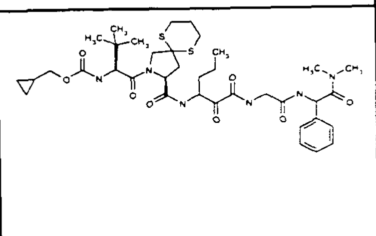
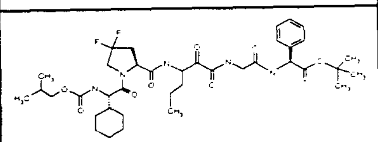
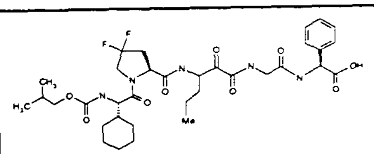
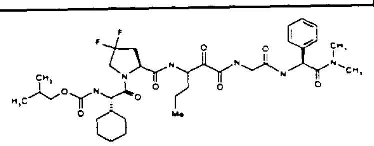
190		823.0945
191		865.1758
192		865.1758
193		817.0876
194		817.0876
195		1606.121
196		1606.121

Table 2

197		1638.12
198		1638.12
199		775.0063
200		775.0063
201		763.887
202		707.7786
203		734.848

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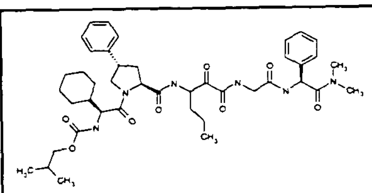
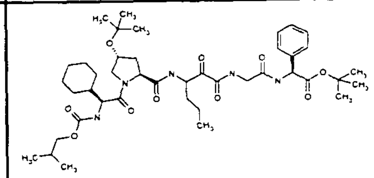
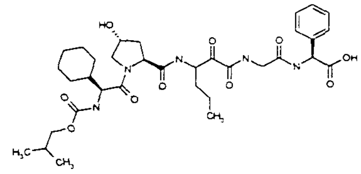
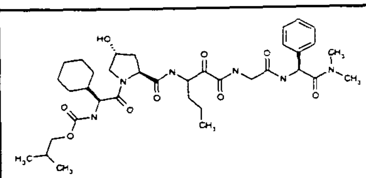
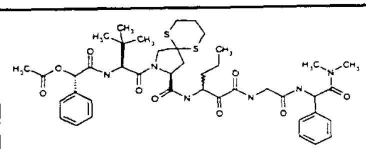
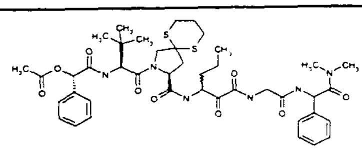
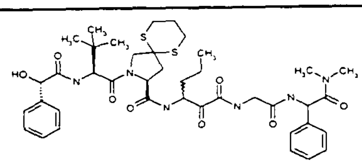
204		774.9659
205		800.0139
206		687.7971
207		714.8666
208		853.0774
209		853.0774
210		811.0398

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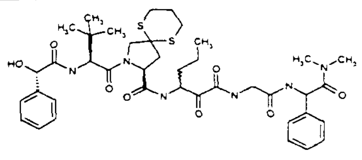
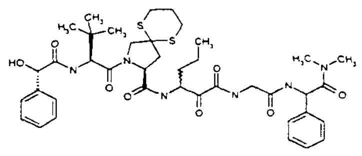
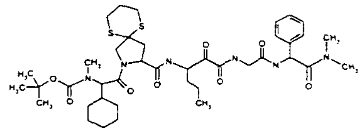
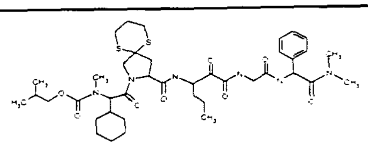
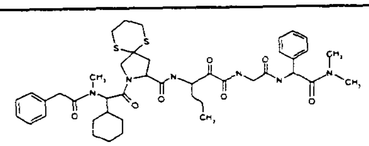
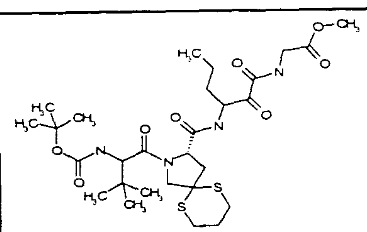
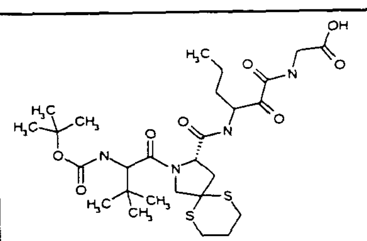
211		811.0398
212		811.0398
213		817.0876
214		817.0876
215		835.1057
216		630.8288
217		616.8018

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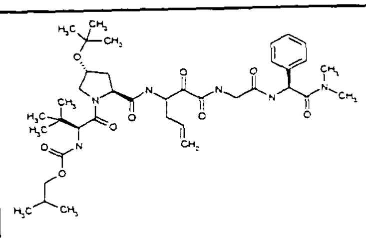
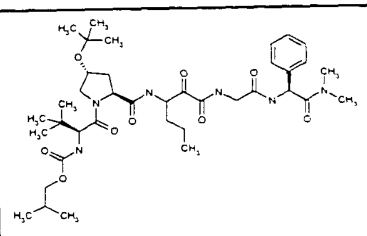
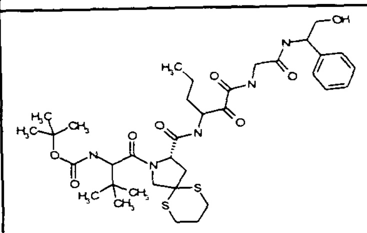
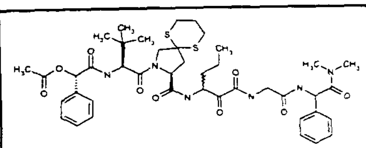
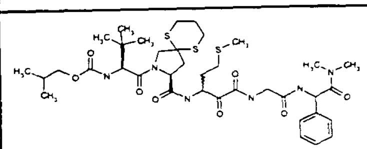
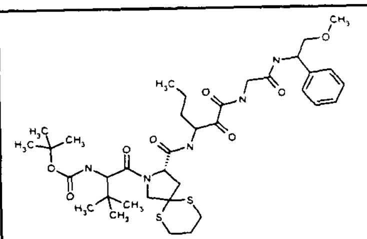
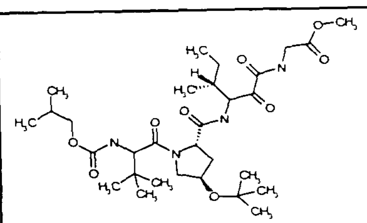
218		742.9208
219		744.9367
220		735.9694
221		853.0774
222		809.0862
223		749.9965
224		612.7703

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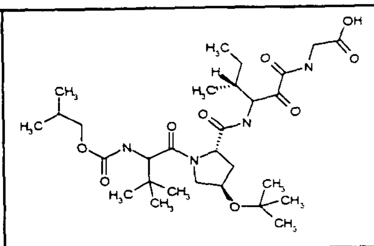
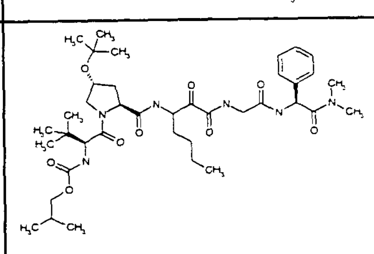
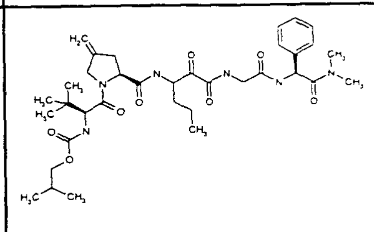
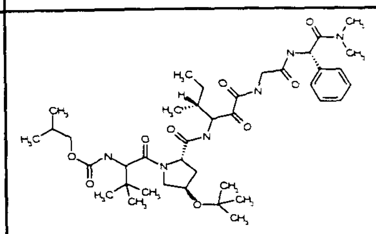
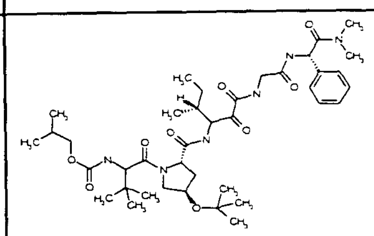
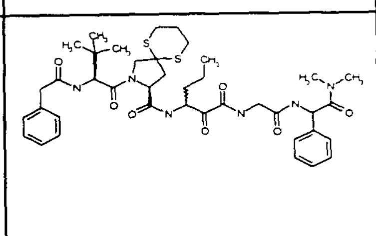
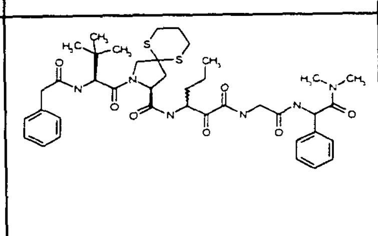
225		598.7432
226		758.9638
227		684.8401
228		758.9638
229		758.9638
230		795.0404
231		795.0404

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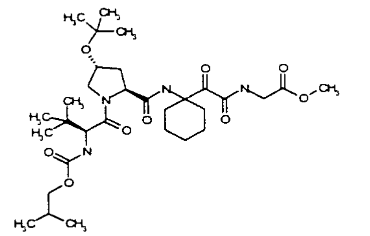
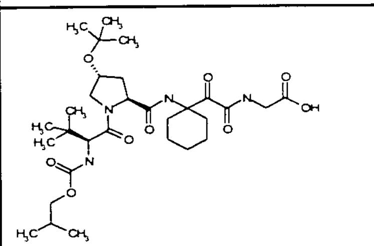
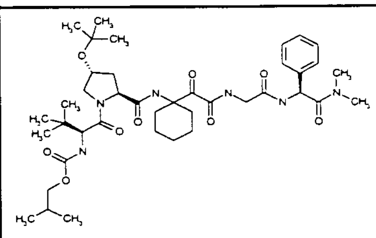
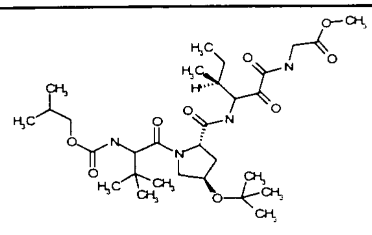
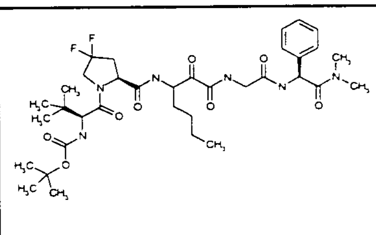
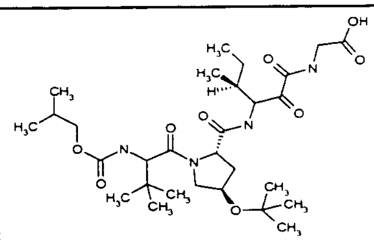
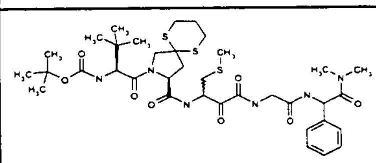
232		624.7815
233		610.7544
234		770.9749
235		612.7703
236		722.8369
237		598.7432
238		795.0592

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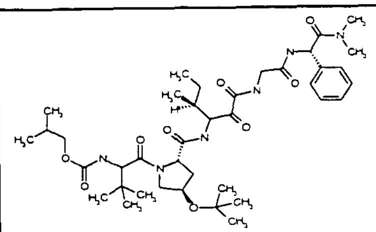
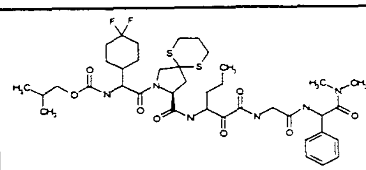
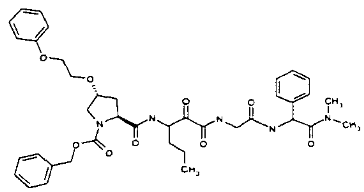
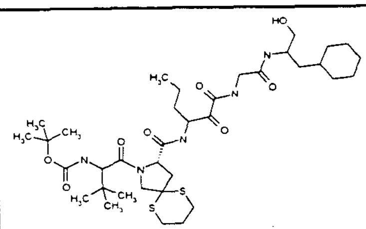
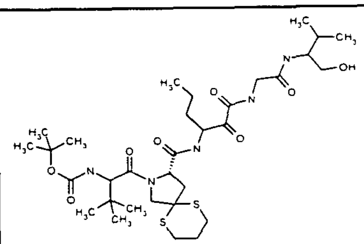
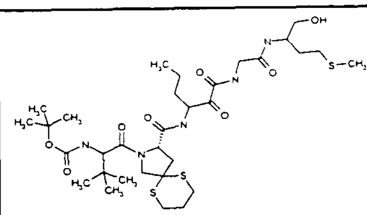
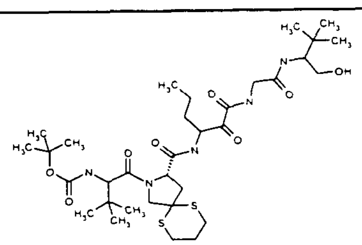
239		758.9638
240		839.0414
241		729.8375
242		756.0443
243		701.9518
244		734.0159
245		715.9789

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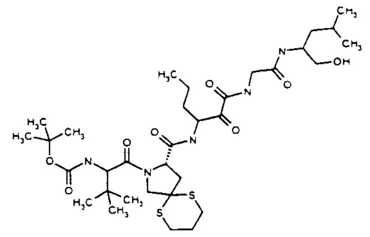
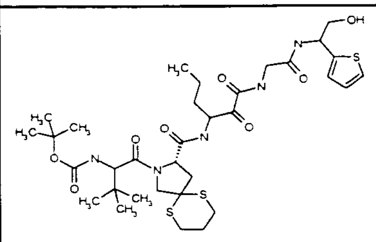
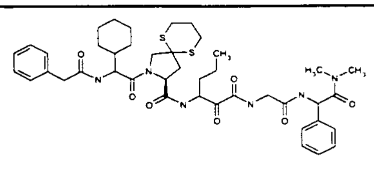
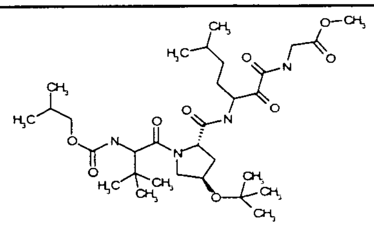
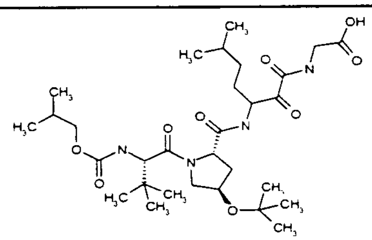
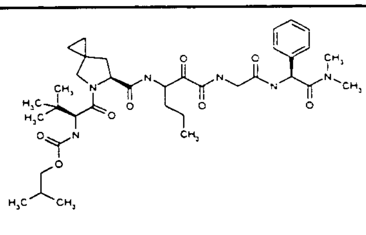
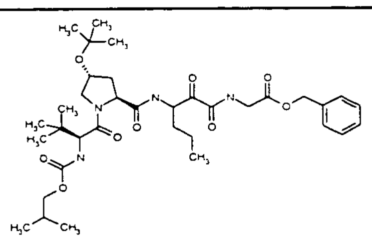
246		715.9789
247		741.9951
248		821.0786
249		626.7974
250		612.7703
251		698.8672
252		674.842

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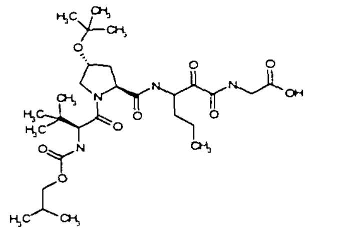
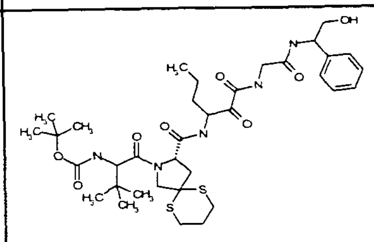
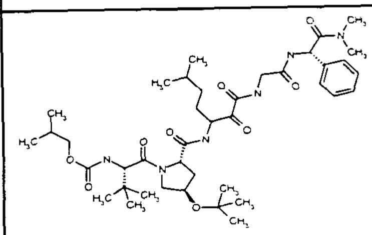
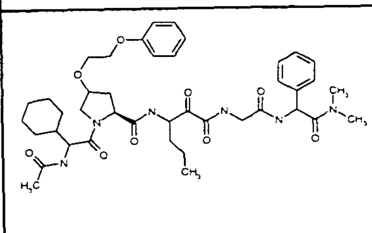
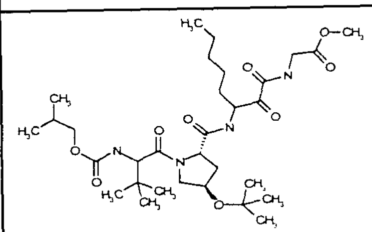
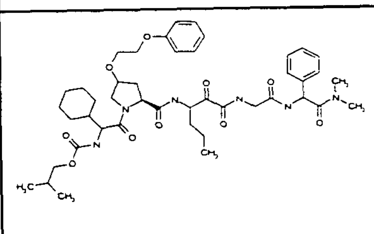
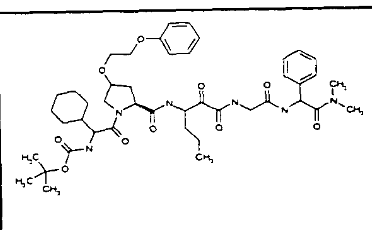
253		584.7162
254		735.9694
255		772.9909
256		776.9383
257		626.7974
258		835.0189
259		835.0189

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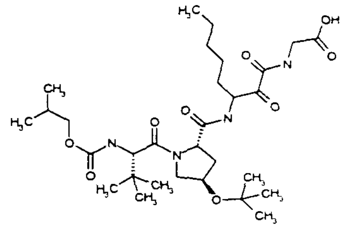
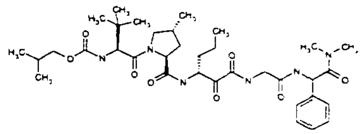
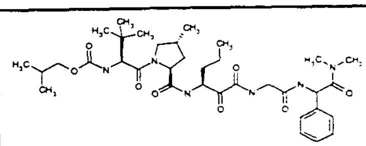
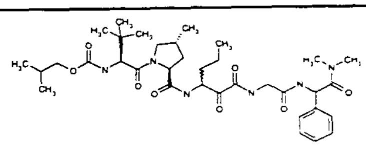
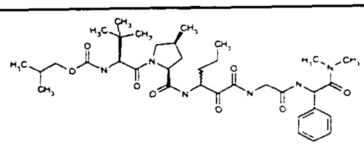
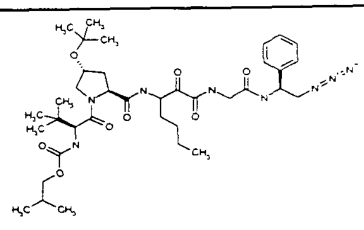
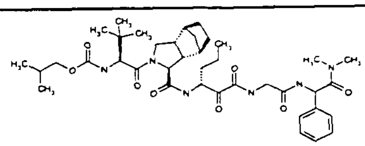
260		612.7703
261		686.856
262		686.856
263		686.856
264		686.856
265		742.9236
266		738.9325

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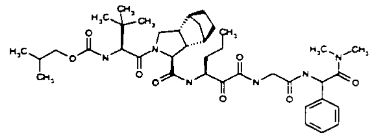
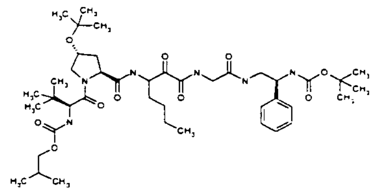
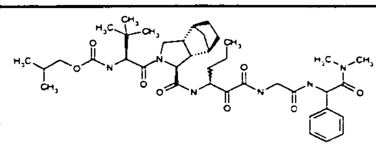
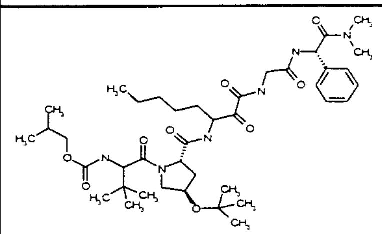
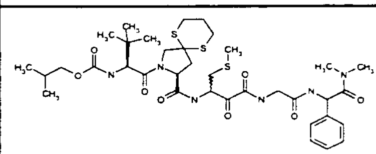
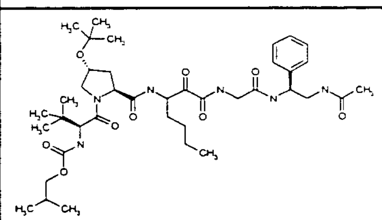
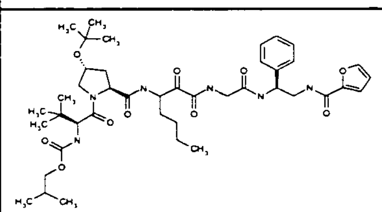
267		738.9325
268		817.0444
269		738.9325
270		772.9909
271		795.0592
272		758.9638
273		810.9966

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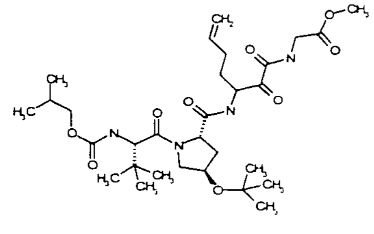
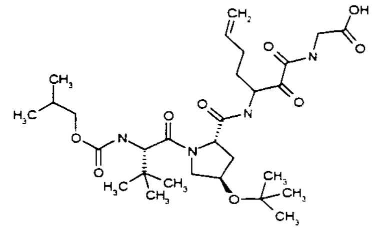
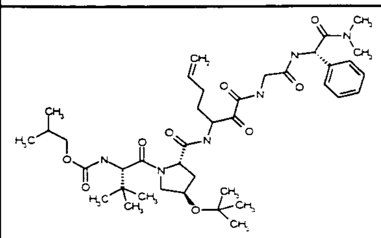
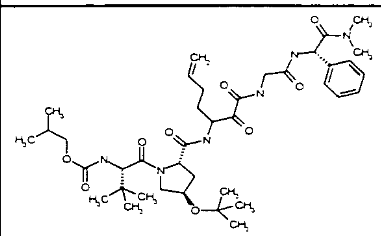
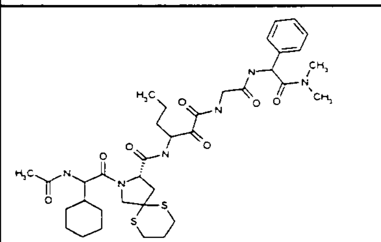
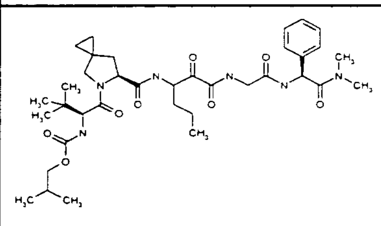
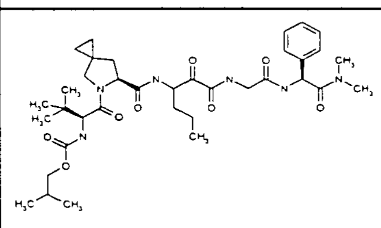
274		610.7544
275		596.7273
276		756.9479
277		756.9479
278		744.9799
279		698.8672
280		698.8672

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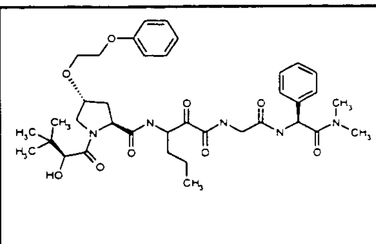
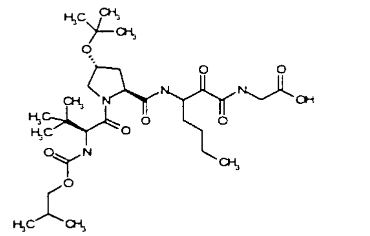
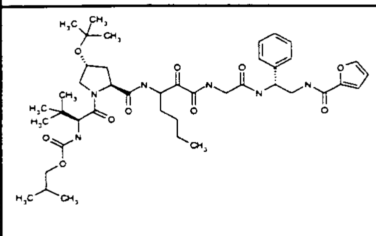
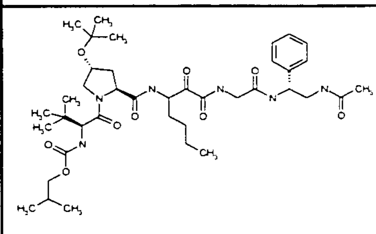
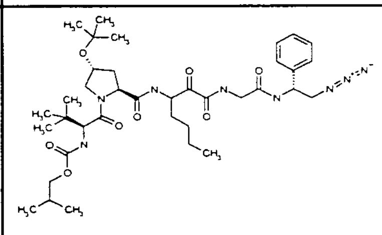
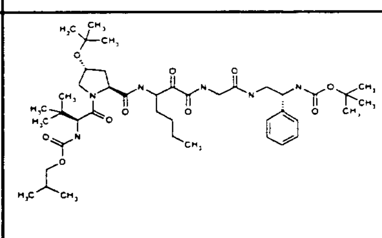
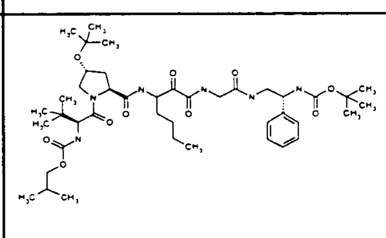
281		709.8471
282		598.7432
283		810.9966
284		758.9638
285		742.9236
286		817.0444
287		817.0444

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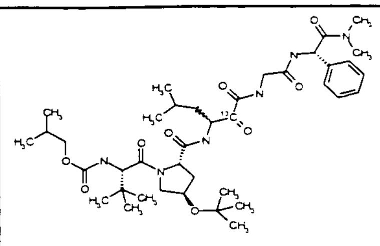
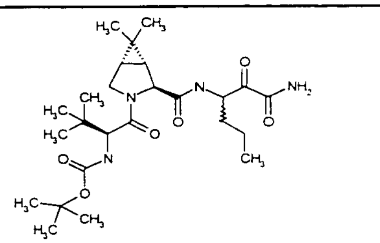
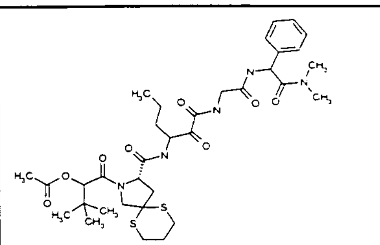
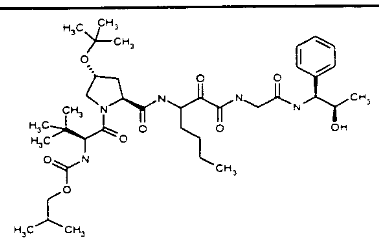
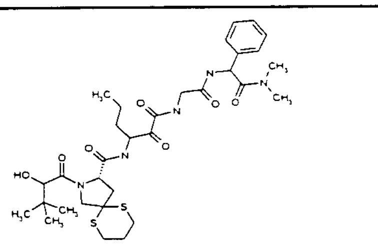
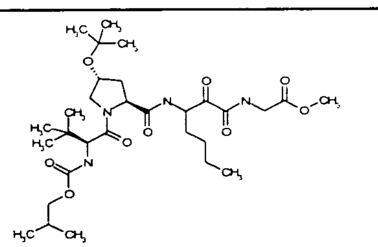
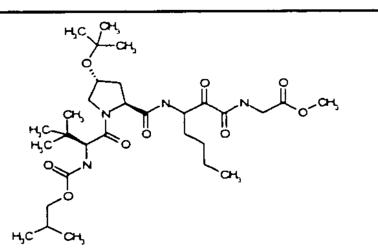
288		759.9526
289		494.6367
290		719.9263
291		731.938
292		677.8887
293		612.7703
294		612.7703

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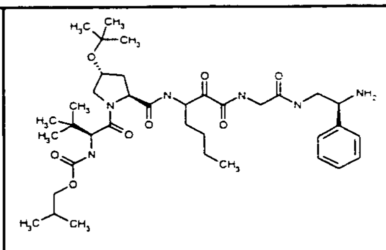
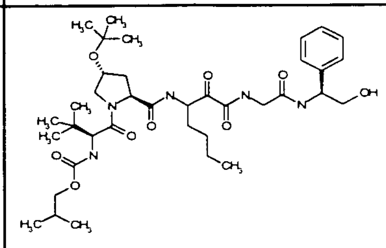
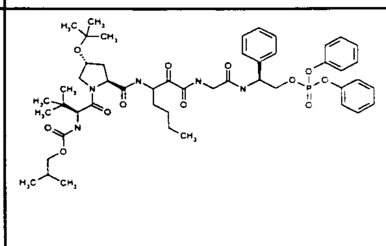
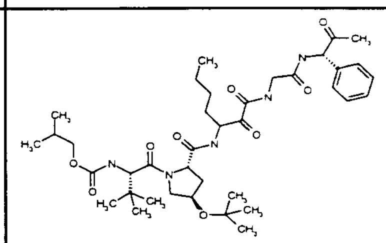
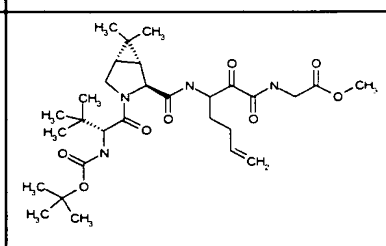
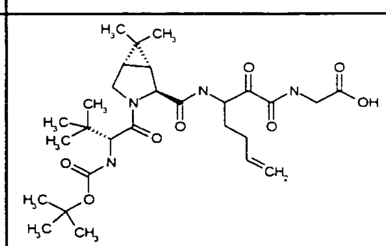
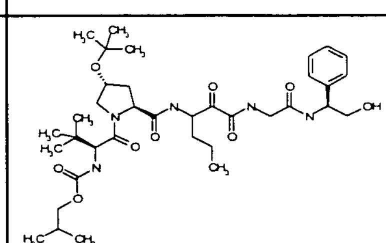
295		716.9261
296		717.9109
297		950.0884
298		729.9221
299		578.712
300		564.6849
301		703.8838

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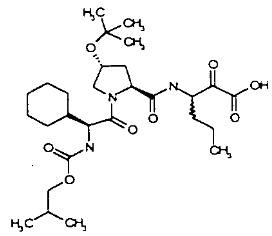
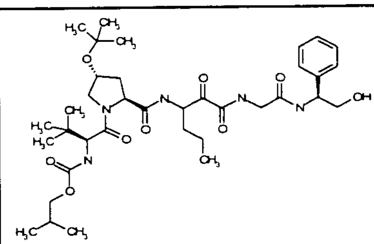
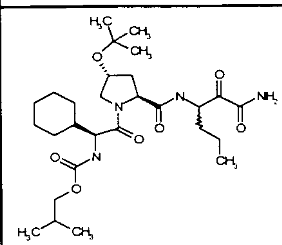
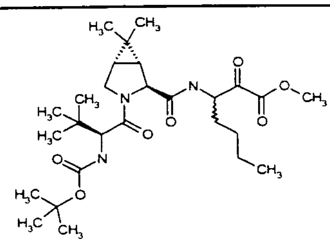
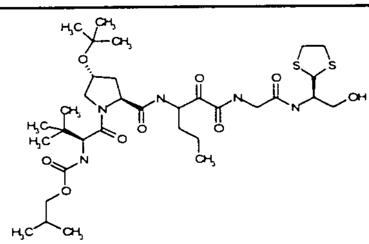
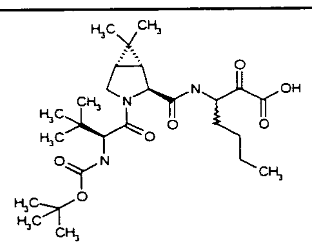
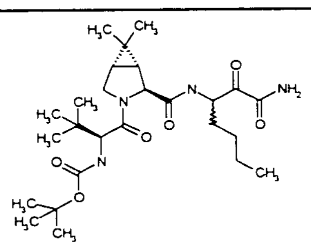
302		553.7021
303		703.8838
304		552.7173
305		523.6756
306		731.9783
307		509.6485
308		508.6638

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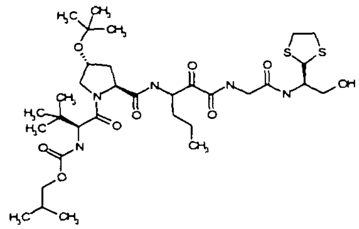
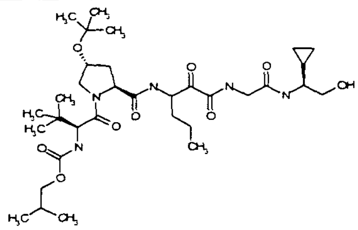
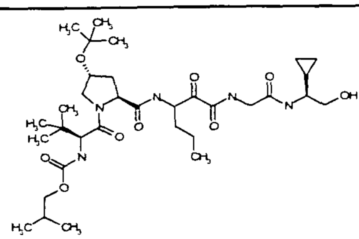
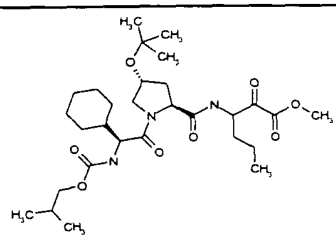
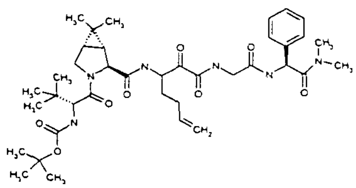
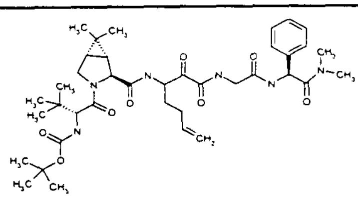
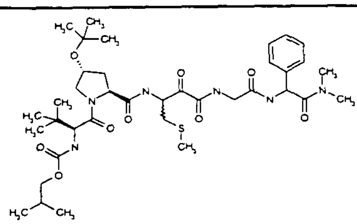
309		731.9783
310		667.8503
311		667.8503
312		567.7292
313		724.9054
314		724.9054
315		762.9736

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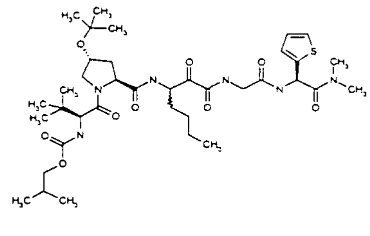
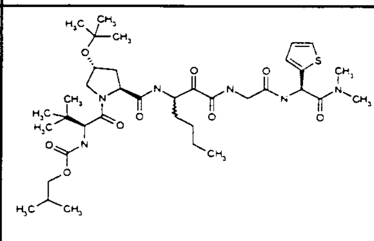
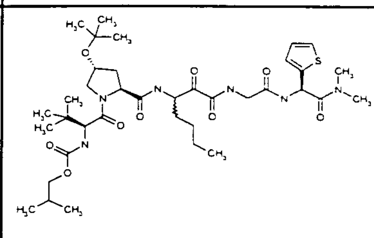
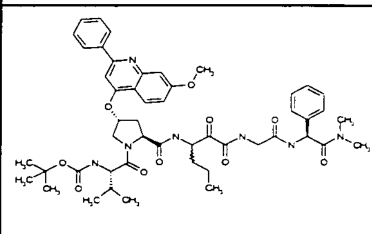
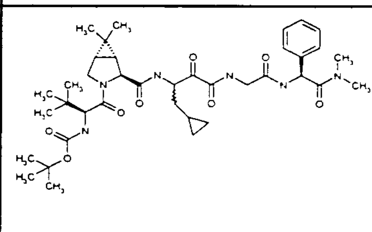
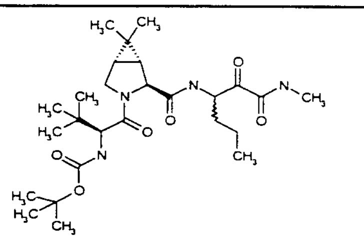
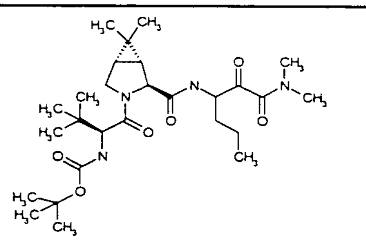
316		764.9896
317		764.9896
318		764.9896
319		908.0734
320		724.9054
321		508.6638
322		522.6909

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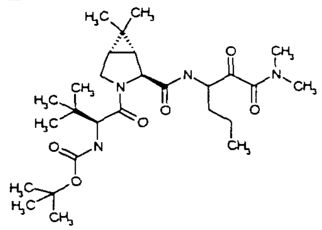
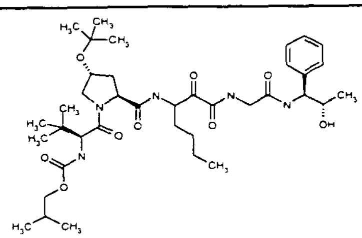
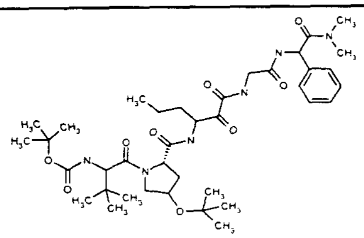
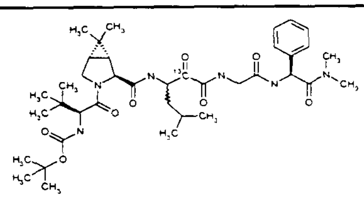
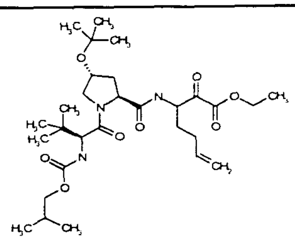
323		522.6909
324		731.938
325		744.9367
326		727.9102
327		567.7292

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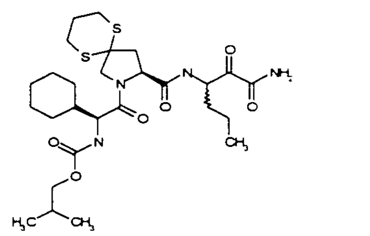
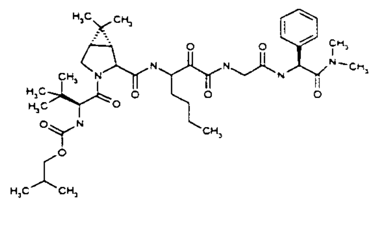
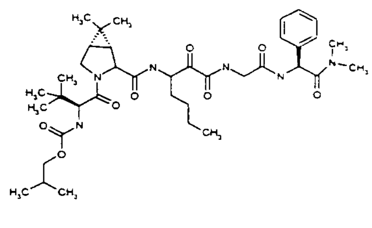
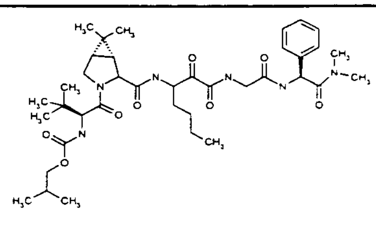
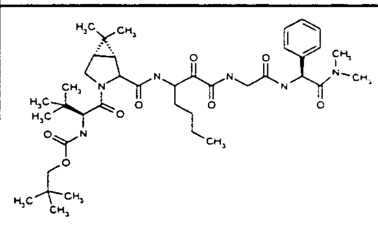
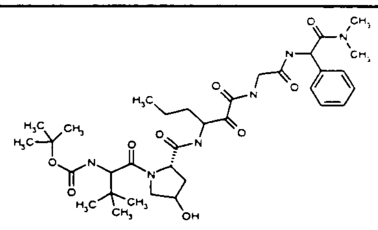
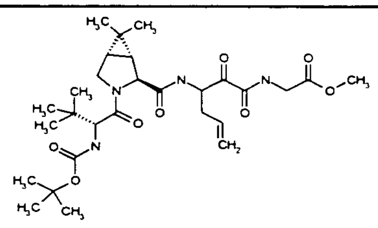
328		584.8029
329		726.9214
330		726.9214
331		726.9214
332		740.9484
333		688.8284
334		564.6849

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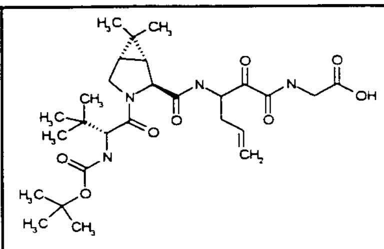
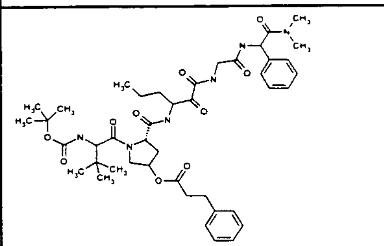
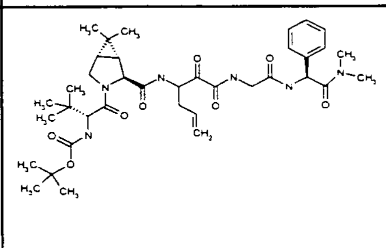
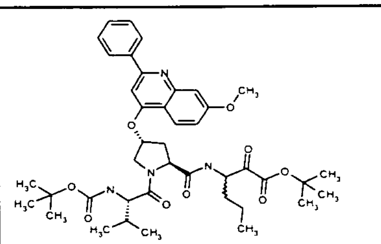
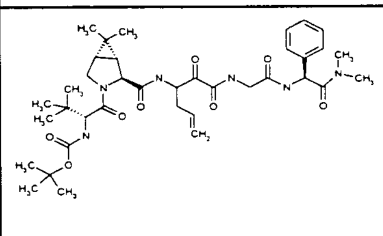
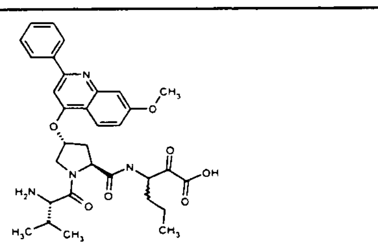
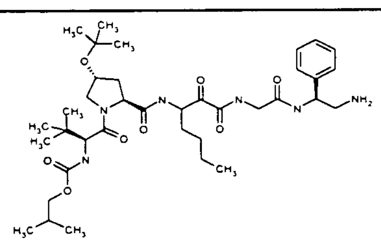
335		550.6578
336		820.9918
337		710.8784
338		746.9089
339		710.8784
340		590.6823
341		716.9261

Table 2

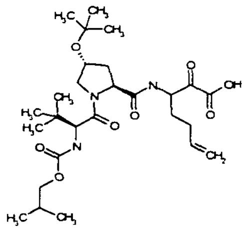
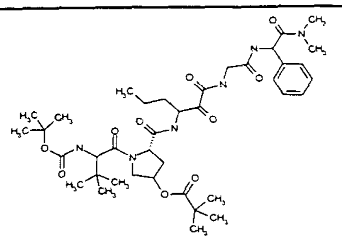
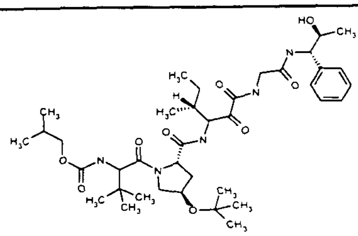
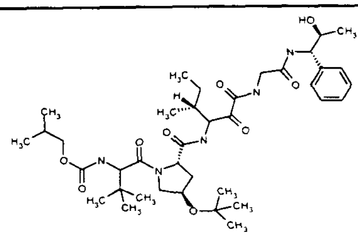
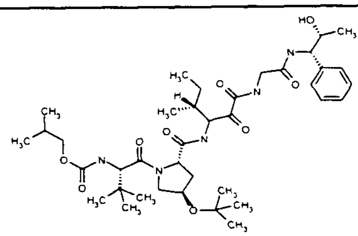
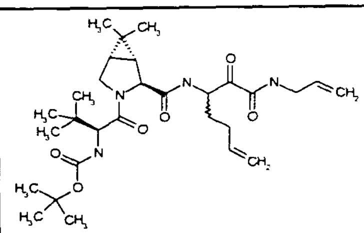
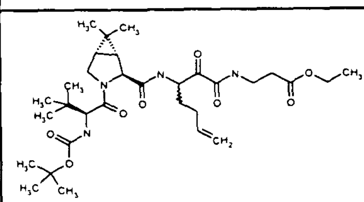
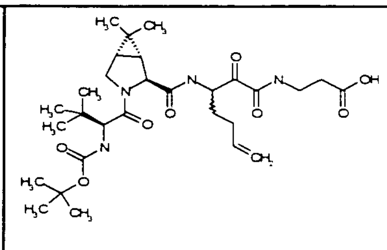
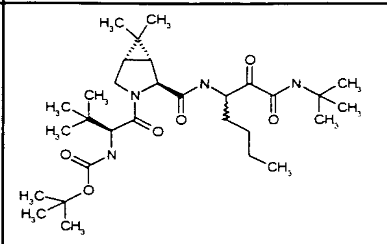
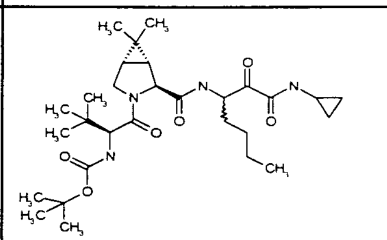
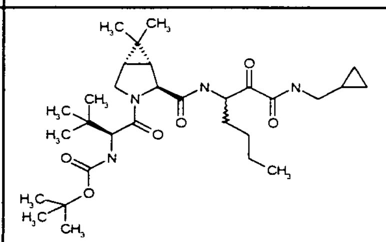
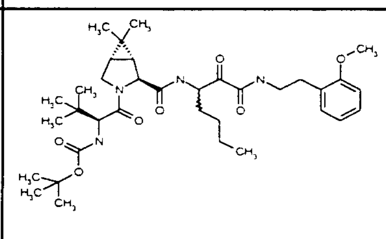
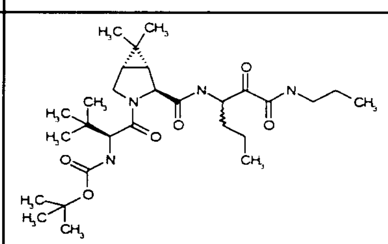
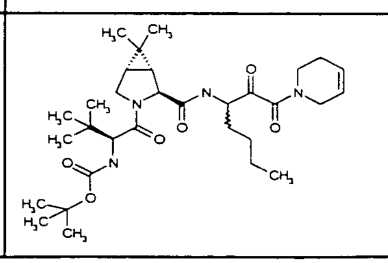
342		539.675
343		772.9473
344		731.938
345		731.938
346		731.938
347		546.7132
348		606.7662

Table 2

349		578.712
350		564.7722
351		548.7291
352		562.7562
353		642.8432
354		536.718
355		574.7673

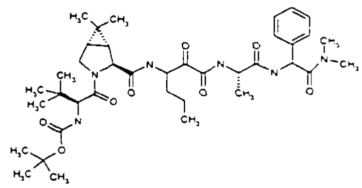
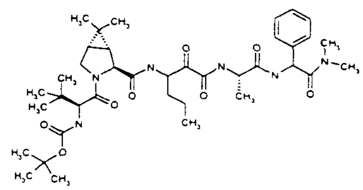
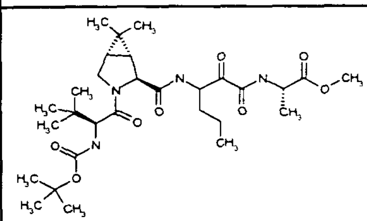
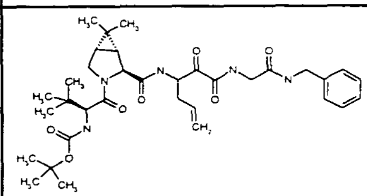
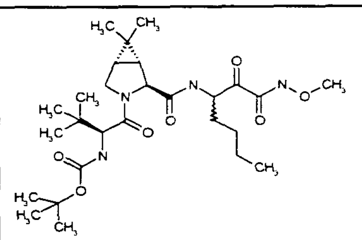
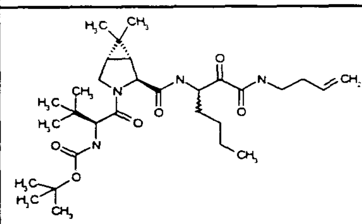
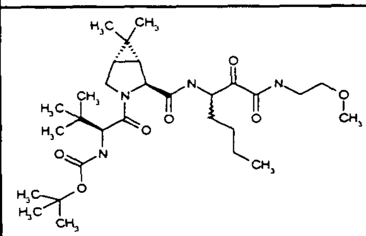
356		726.9214
357		726.9214
358		580.7279
359		639.799
360		538.6902
361		562.7562
362		566.7444

Table 4

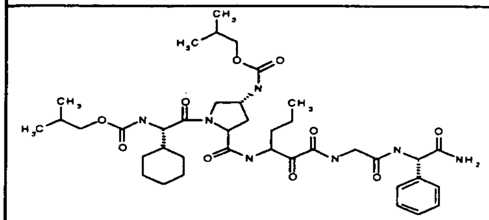
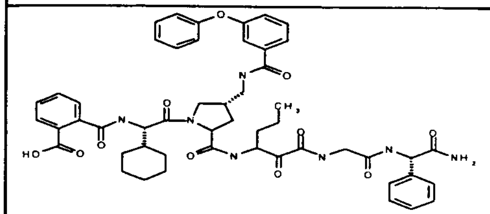
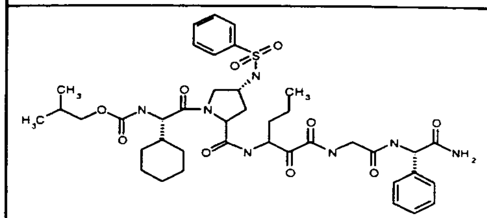
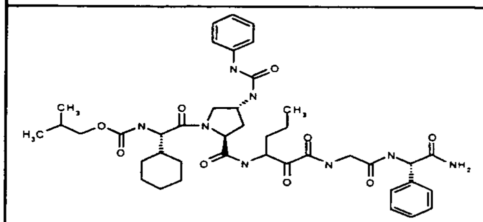
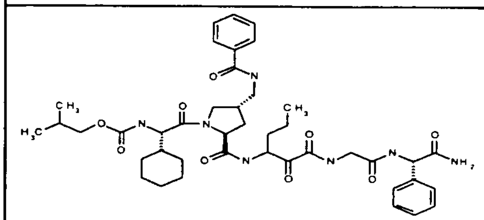
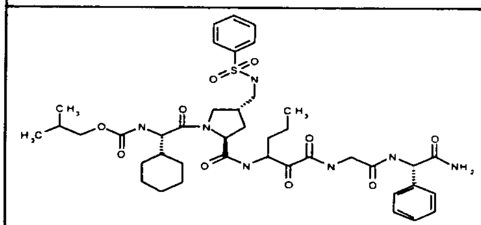
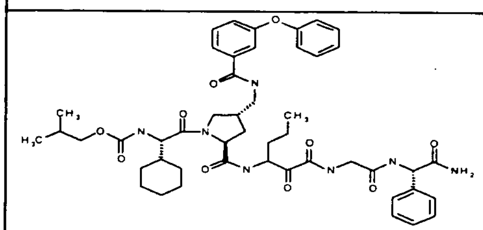
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHiBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2-CO2)PhCO-G(Chx)-P(4t-MeNHCOPh(3-OPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-UreaPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh(3-OPh))-nV-(CO)-G-G(Ph)-Am	B

Table 4

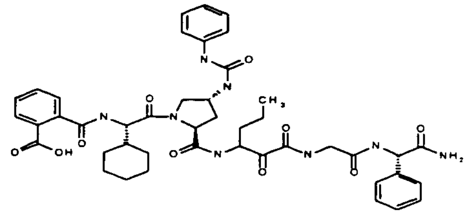
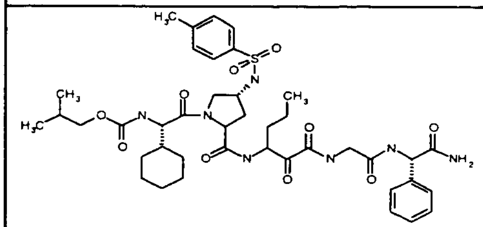
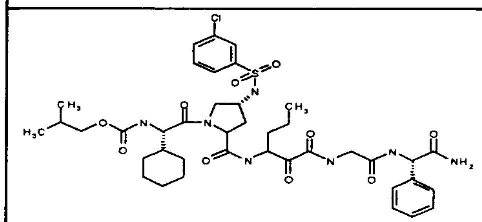
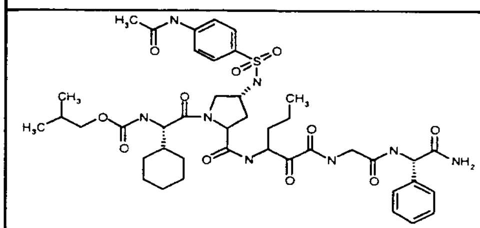
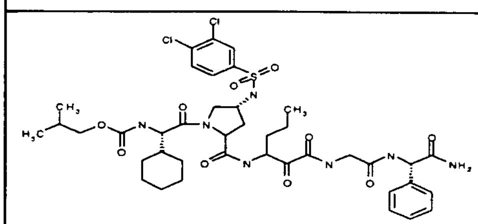
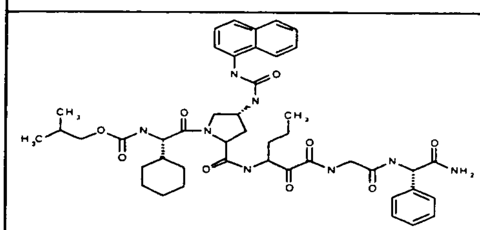
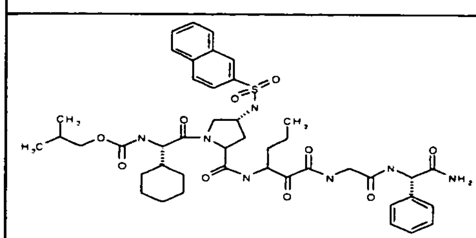
STRUCTURE	NAME	Ki* Range
	(2-CO2)PhCO-G(chx)-P(4t-UreaPh)-nV-(CO)-G-G(ph)-Am	C
	iBoc-G(Chx)-P(4t-NHSO2-(4Me)Ph)-nV(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(3Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(4-NHAc)Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2-(3,4-diCl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-1-Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-2-Np)-nV-(CO)-G-G(Ph)-Am	B

Table 4

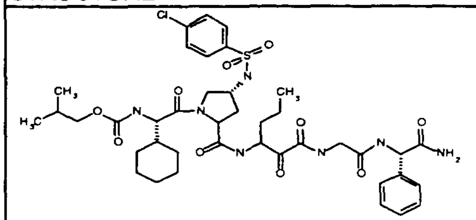
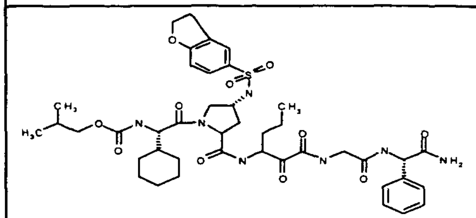
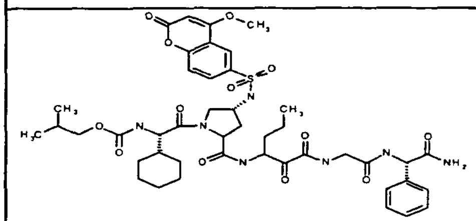
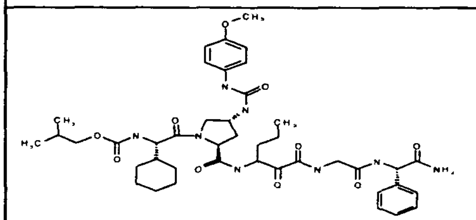
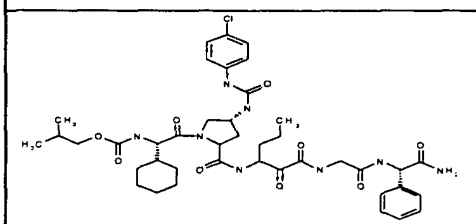
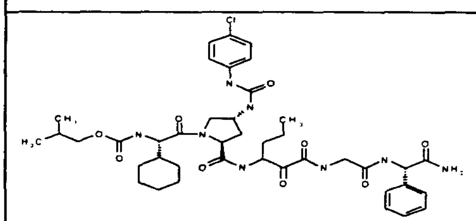
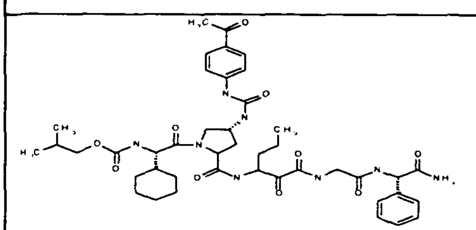
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHSO2-(4Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-5(2,3-dihydrobenzofuran))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-6(4-OMe)Courmarin)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	C
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B

Table 4

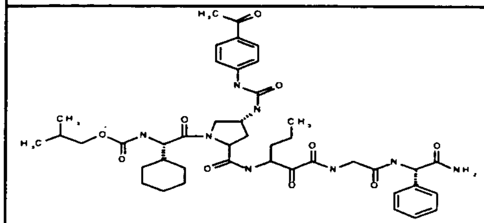
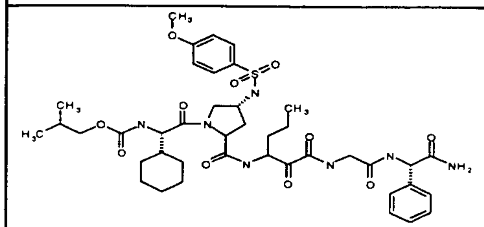
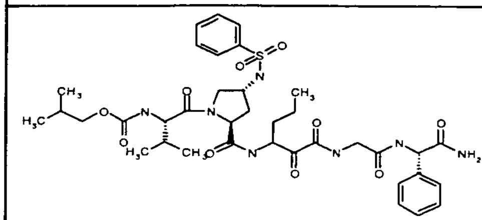
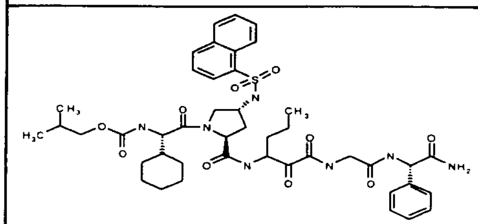
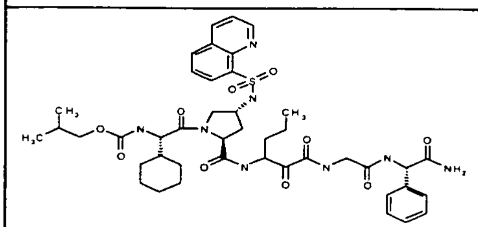
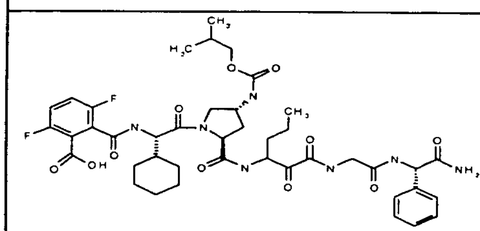
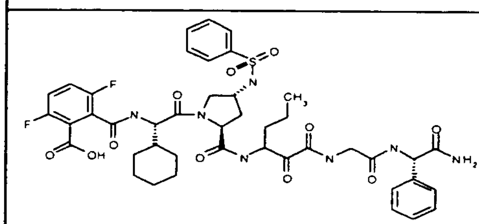
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-V-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-1Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-8-Quinoline)-nV-(CO)-G-G(Ph)-Am	B
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A

Table 4

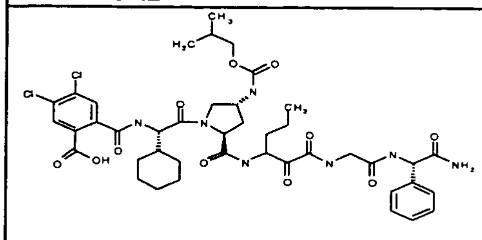
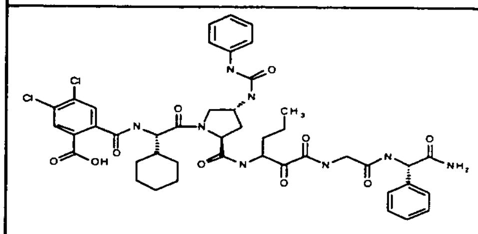
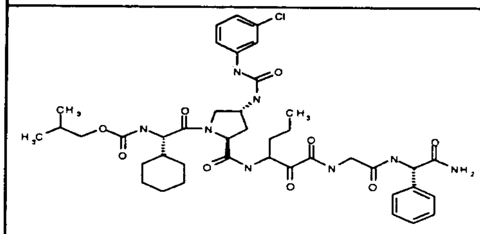
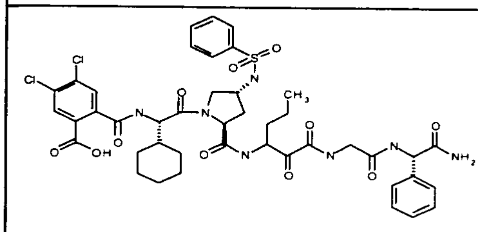
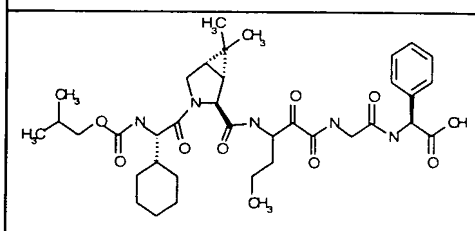
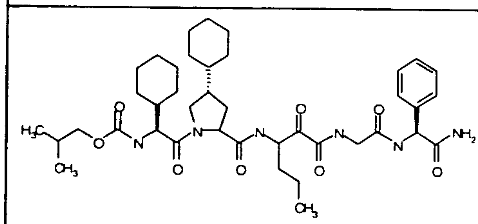
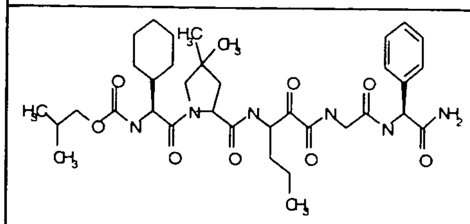
STRUCTURE	NAME	Ki* Range
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-UreaPh)-nV(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-(3-Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(3,4-iPr)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-P(4t-Chx)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-diMe)-nV-(CO)-G-G(Ph)-Am	A

Table 4

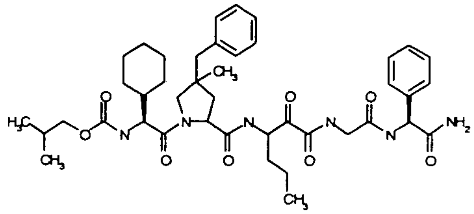
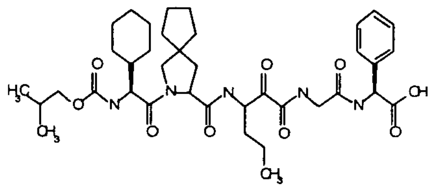
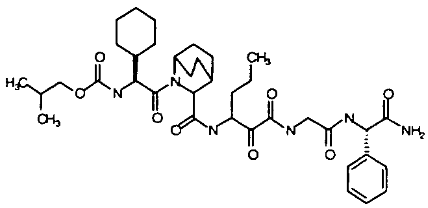
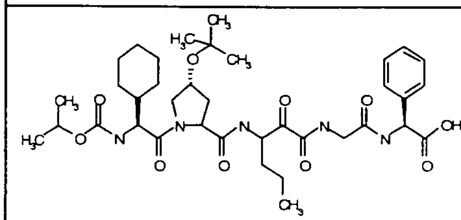
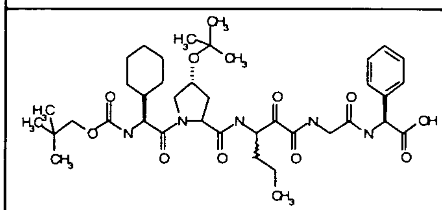
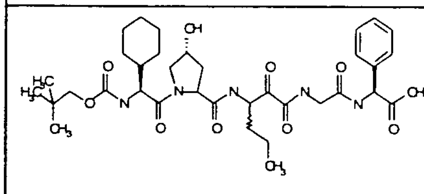
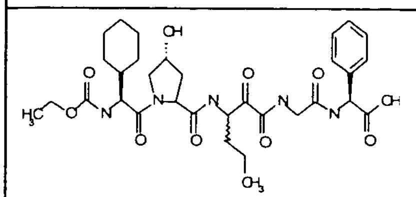
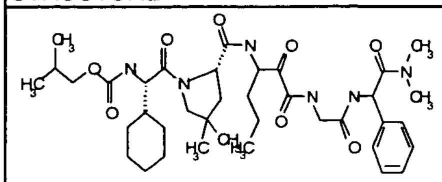
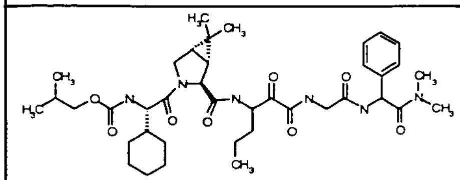
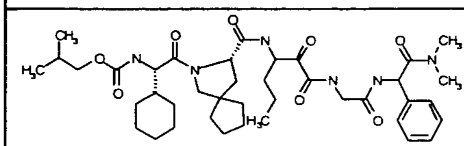
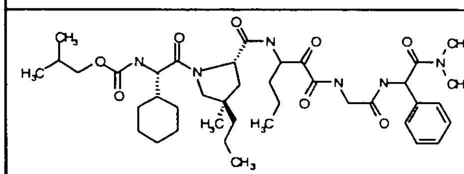
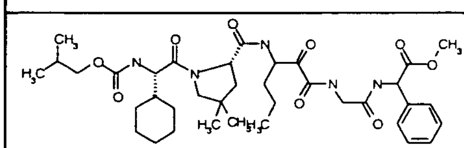
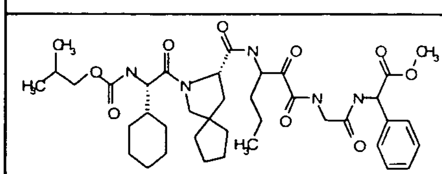
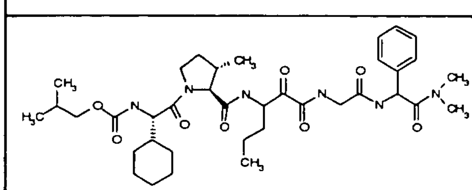
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4-Bn,4-Me)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-spirocyclopentane)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-2-Azabicyclo[2.2.2]octane-3-CO-nV-(CO)-G-G(Ph)-Am	B
	iPrOCO-G(Chx)-P(4-OtBu)-nV-(CO)-G-G(Ph)-OH	A
	Neopentoxy(CO)-G(Chx)-P(4-OtBu)-nV- (CO)-G-G(Ph)-OH	B
	Neopentoxy(CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B
	Ethoxy(CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B

Table 4

STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-iPr)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-spirocyclopentane)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4c-Me,4t-Pr)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)- G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(4-spirocyclopentane)- nV-(CO)-G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(3t-Me)-nV-(CO)- G-G(Ph)-N(Me)2	A

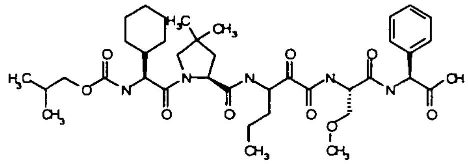
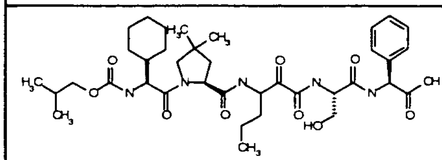
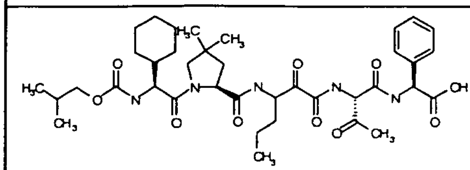
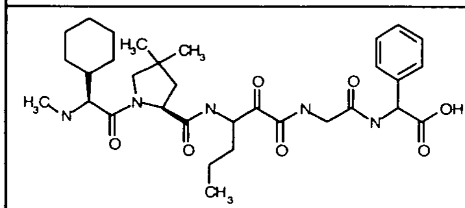
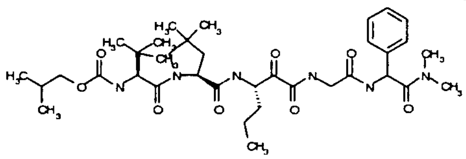
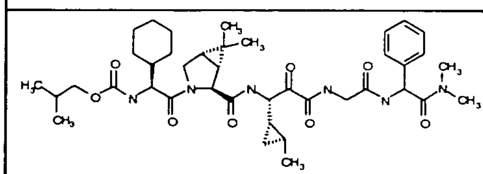
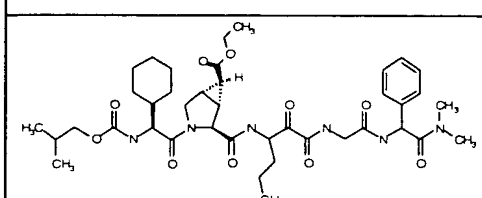
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-S(Me)-G(Ph)-OH	A
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-S-G(Ph)-OH	B
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-G(Ac)-G(Ph)-OH	C
	N-Me-G(Chx)-P(4,4-diMe)-nV-(CO)-G- G(Ph)-CO2H	C
	iBoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-(diMe-cyclopropyl))-G((S,S)-Me-cyclopropyl)-(CO)-G-G(Ph)-N(Me)	A
	iBoc-G(Chx)-P(6S-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

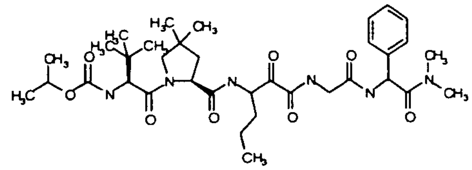
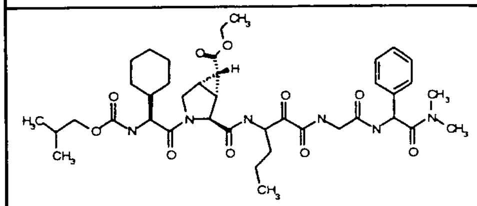
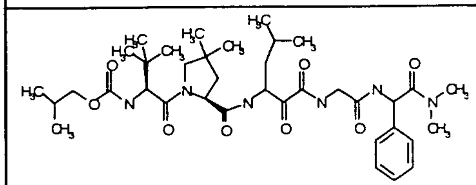
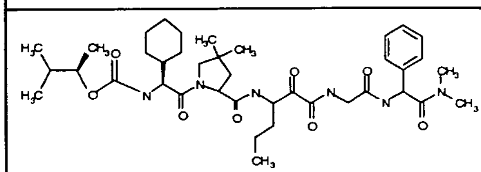
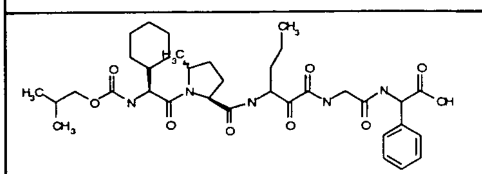
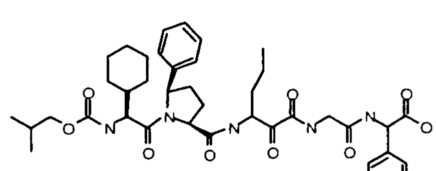
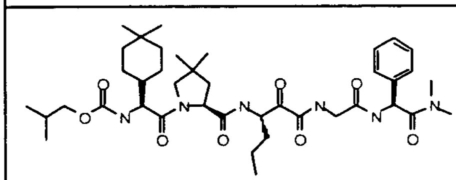
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(6R-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-CO2H	A
	iBoc-G(Chx)-P(5-cis-Ph)-nV-(CO)-G-G(Ph)-CO2H	B
	iBoc-G(4,4-diMeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

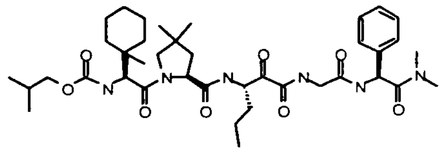
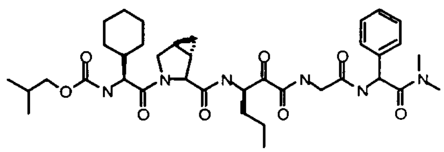
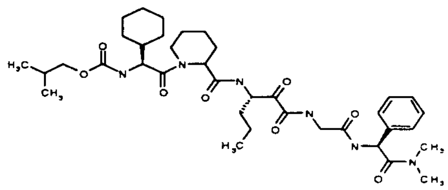
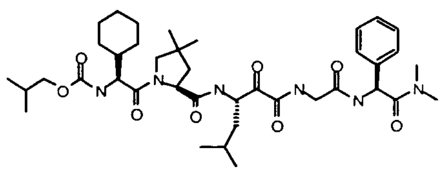
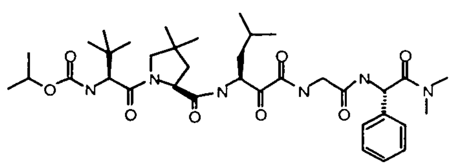
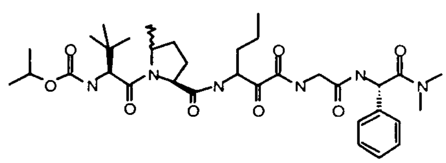
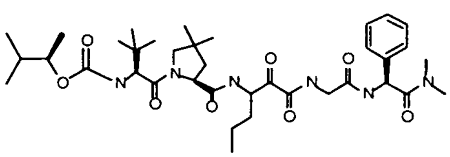
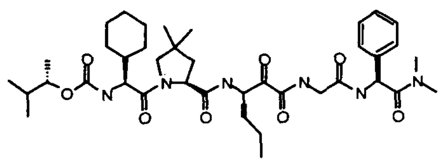
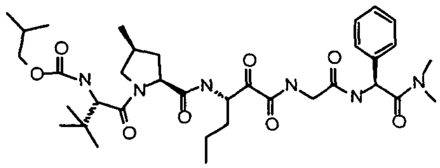
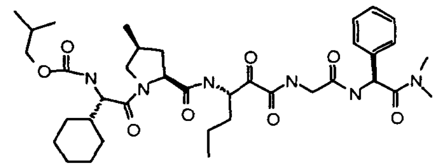
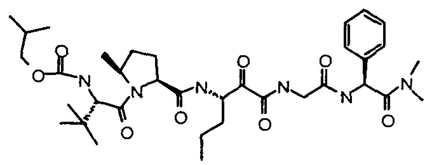
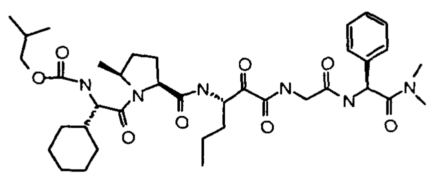
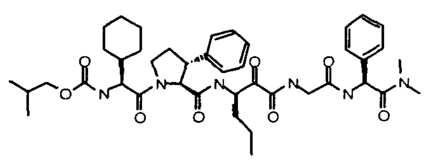
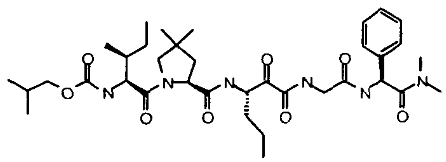
STRUCTURE	NAME	Ki* Range
	iBoc-G(1-MeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-Chg-Pip-nV-(CO)-G-G(Ph)-N(Me)2	C
	iBoc-G(Chx)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

STRUCTURE	NAME	Ki* Range
	(S)-1-MeiBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(t-3Ph)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-allo(Ile)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

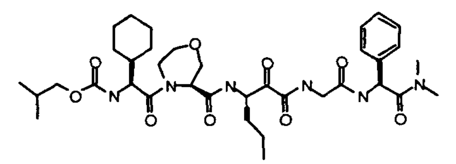
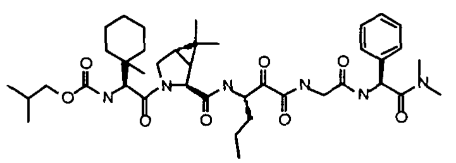
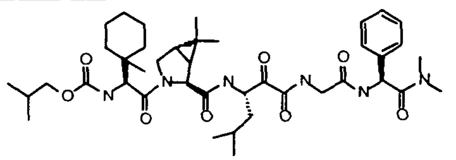
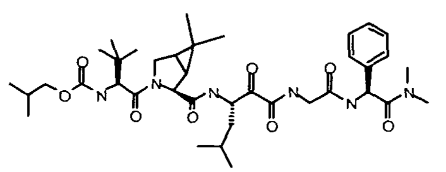
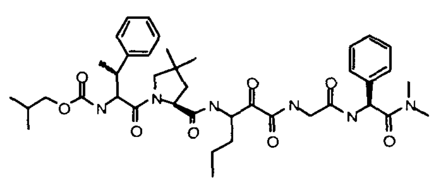
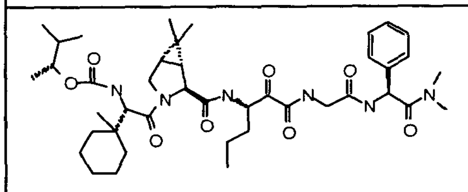
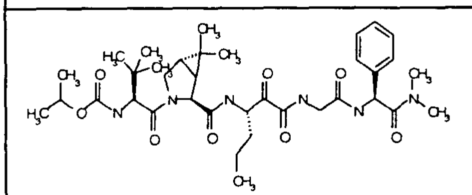
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-Pip(4-morpholino)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-erythro-D,L-F(beta-Me)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P[3,4-(diMe-cyclorpropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

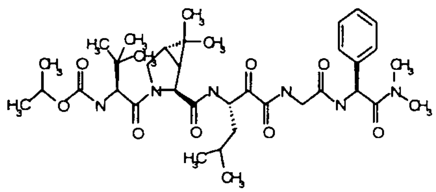
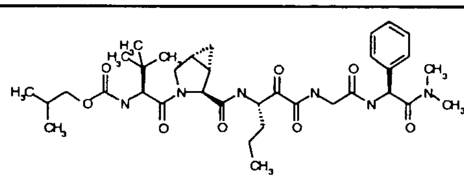
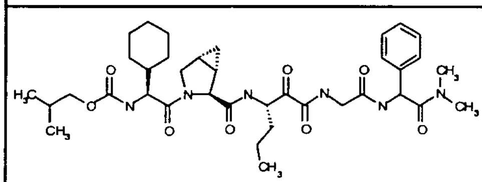
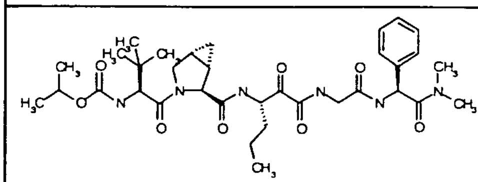
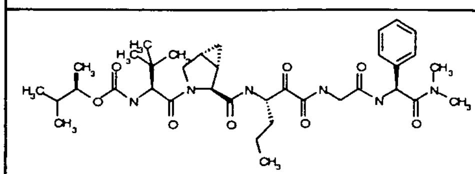
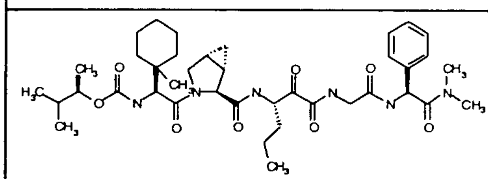
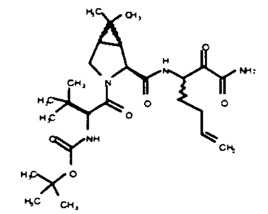
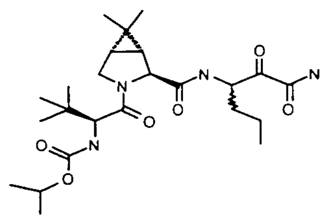
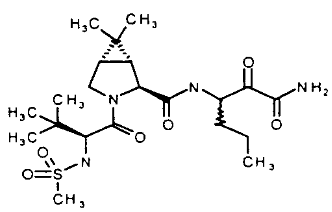
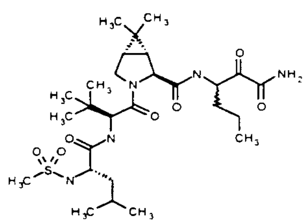
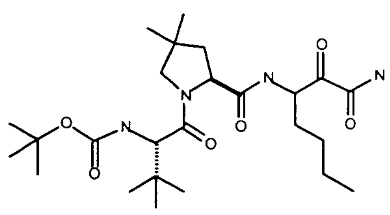
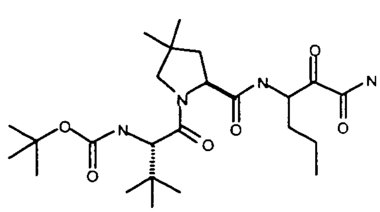
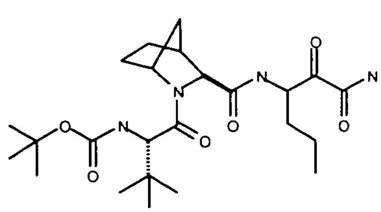
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 5

Structure	MW	Ki* range
	507	B
	481	B
	473	C
	586	B
	497	C
	483	C
	481	C

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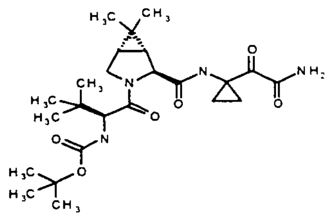
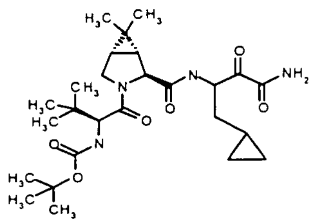
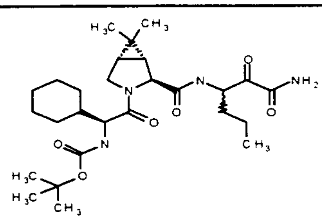
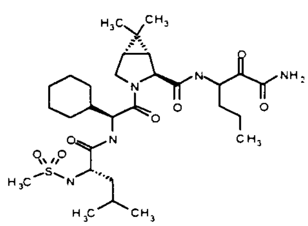
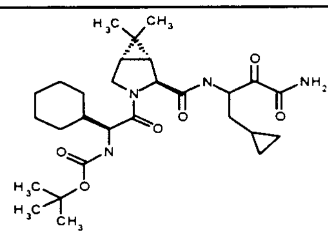
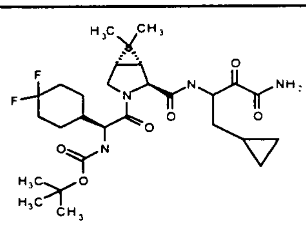
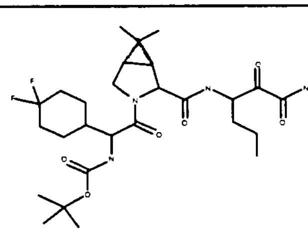
	479	B
	507	A
	521	A
	612	A
	533	A
	569	A
	557	B

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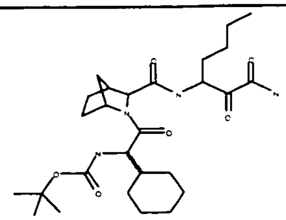
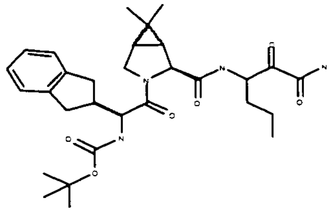
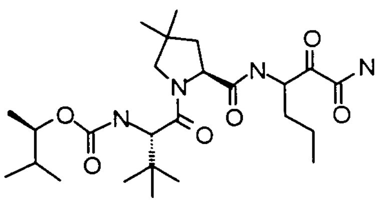
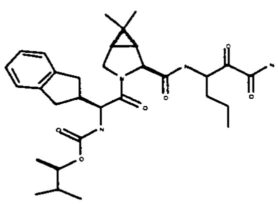
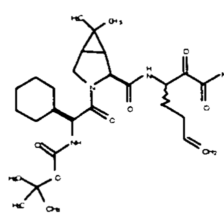
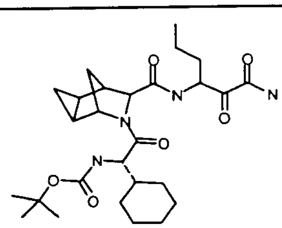
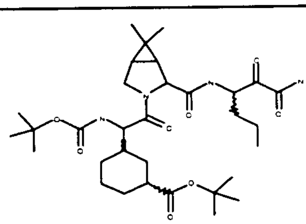
	521	C
	555	A
	497	C
	569	B
	533	B
	519	C
	621	B

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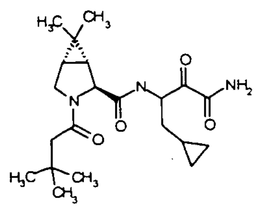
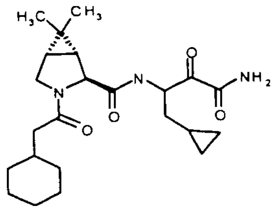
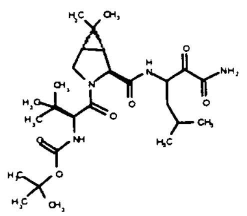
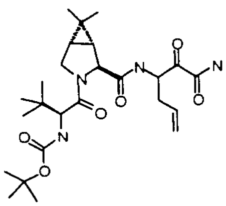
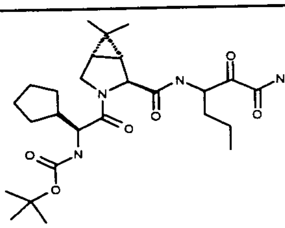
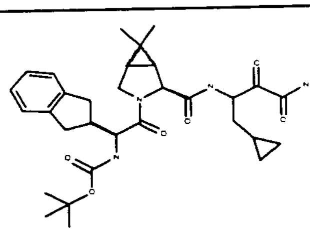
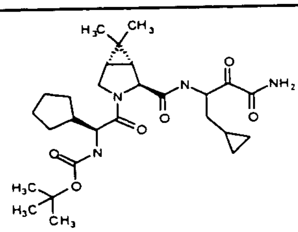
	392	C
	418	C
	509	B
	493	C
	507	B
	567	A
	519	A

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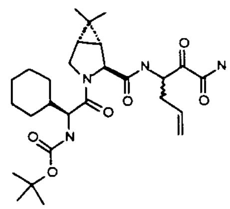
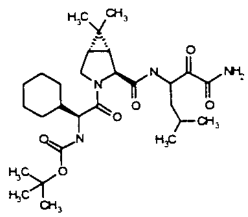
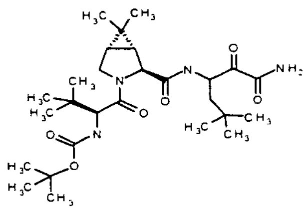
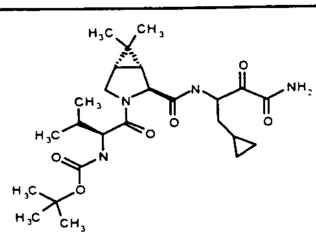
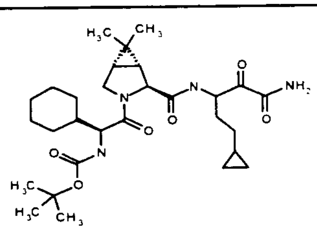
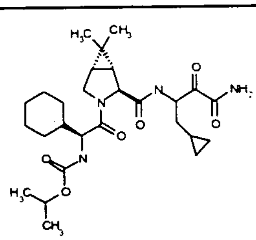
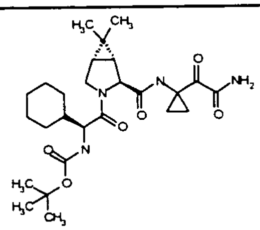
	519	B
	535	B
	523	C
	493	B
	547	B
	519	A
	505	C

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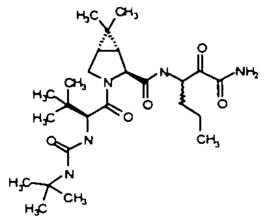
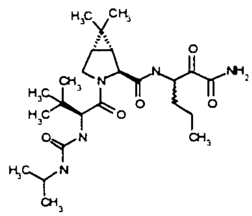
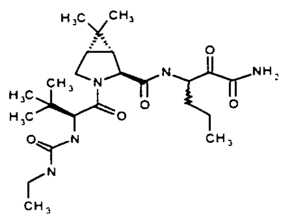
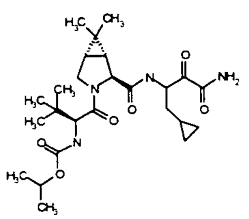
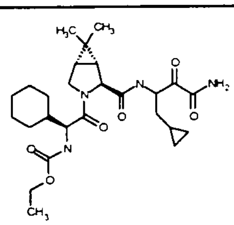
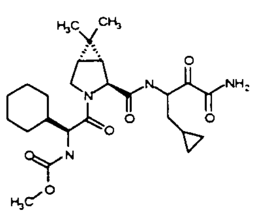
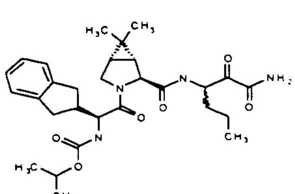
	494	B
	480	B
	466	C
	493	B
	505	B
	491	B
	541	B

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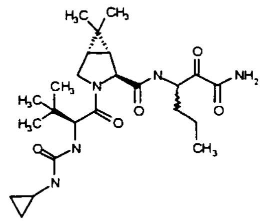
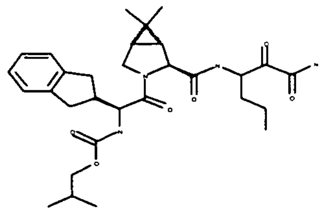
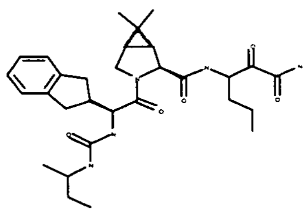
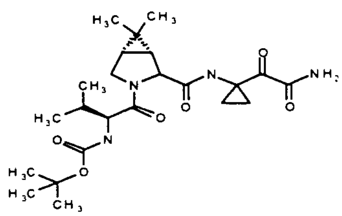
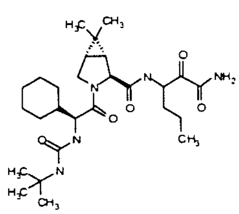
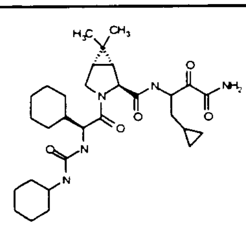
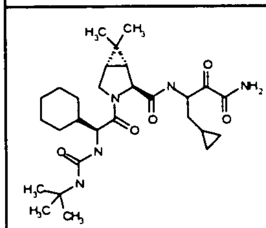
	478	C
	555	B
	554	B
	465	C
	520	A
	558	A
	532	A

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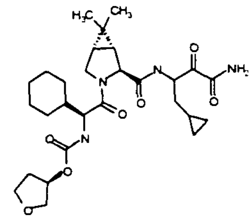
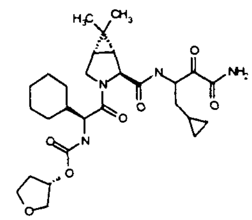
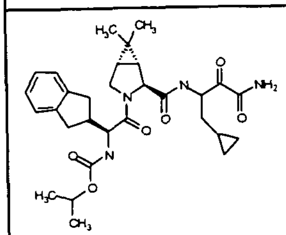
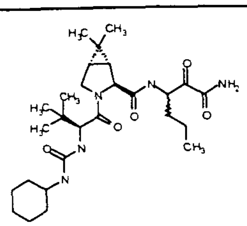
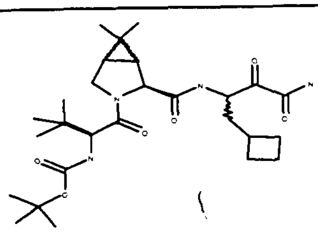
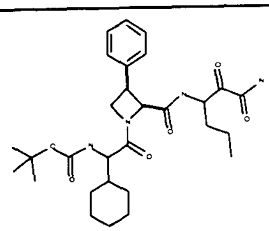
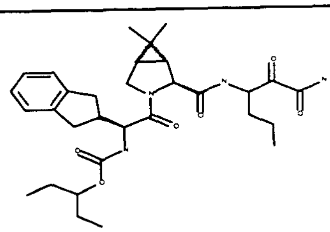
	547	B
	547	B
	553	A
	520	B
	521	A
	543	C
	569	B

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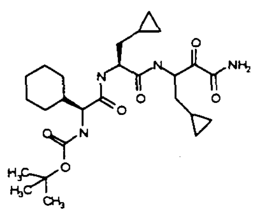
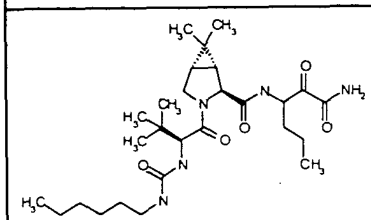
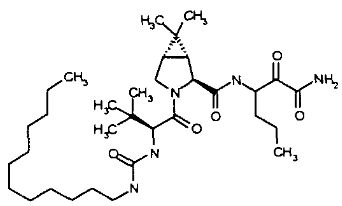
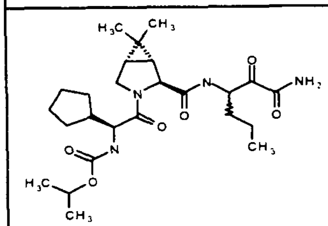
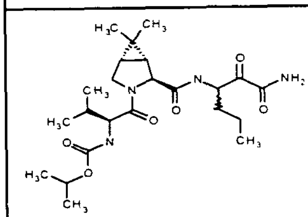
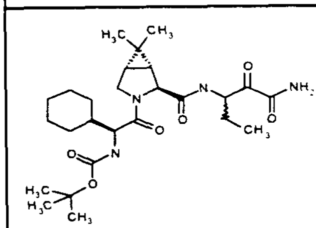
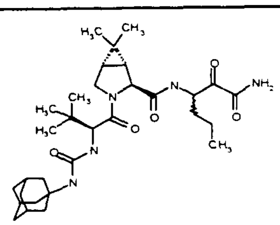
	507	B
	522	B
	606	C
	493	B
	467	C
	507	B
	572	A

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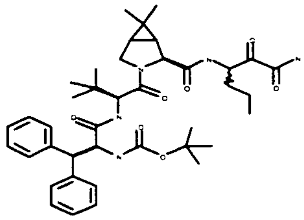
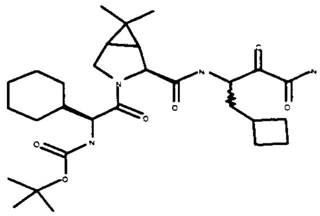
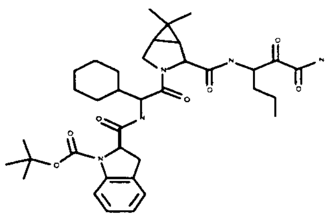
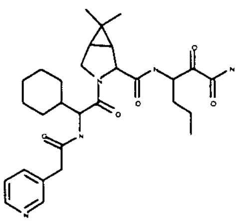
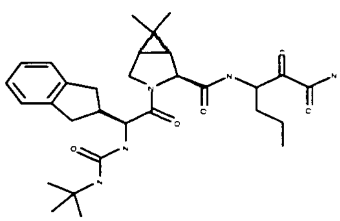
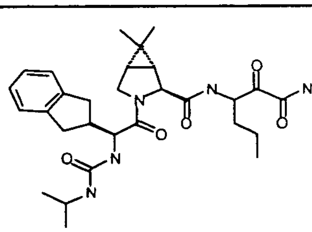
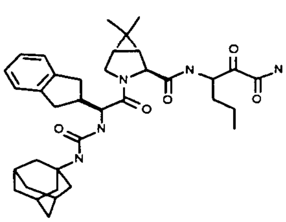
	718	C
	547	A
	666	B
	540	C
	554	B
	540	B
	632	B

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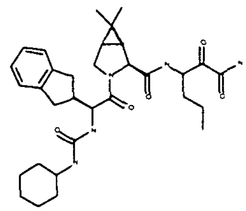
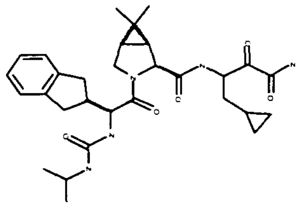
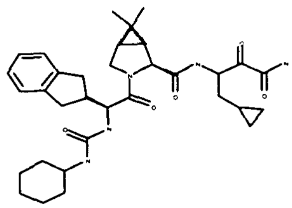
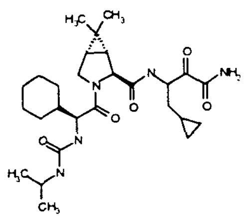
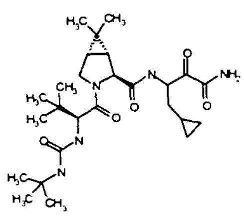
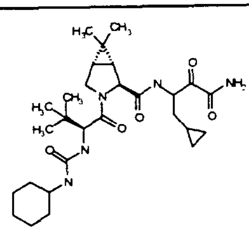
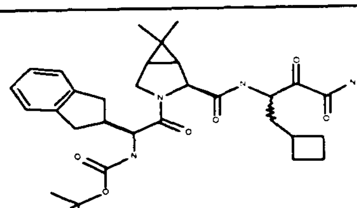
	580	B
	552	A
	592	A
	518	A
	506	A
	532	A
	581	B

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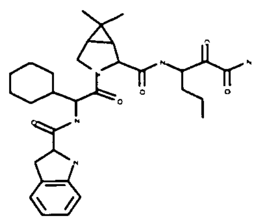
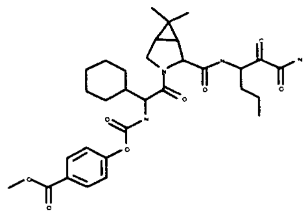
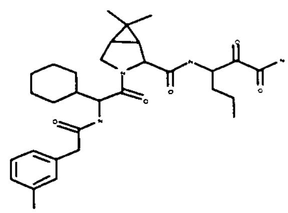
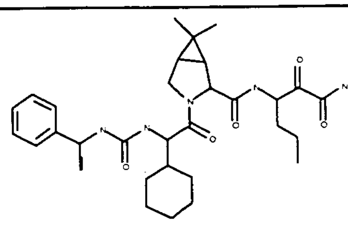
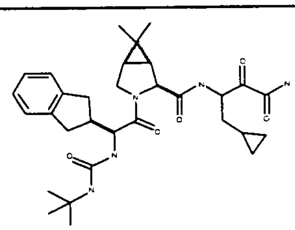
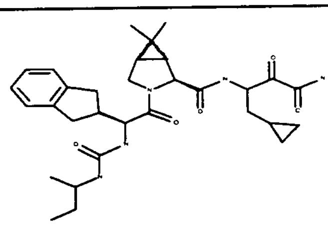
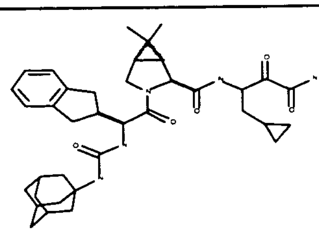
	566	C
	599	B
	553	B
	568	B
	566	A
	566	A
	644	A

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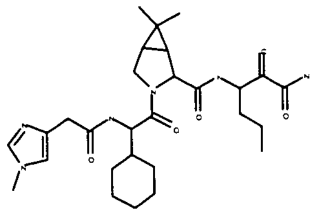
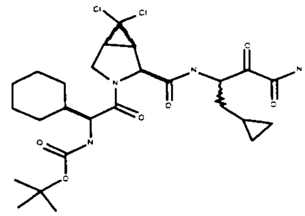
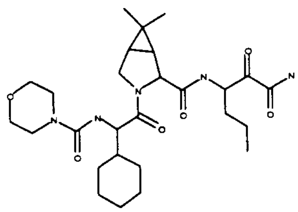
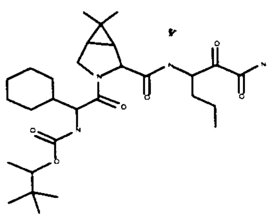
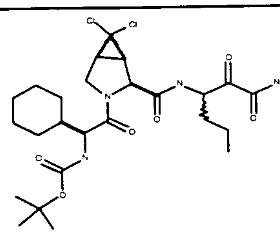
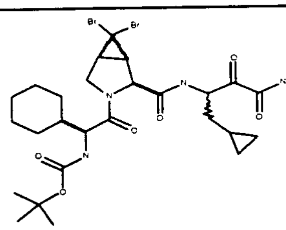
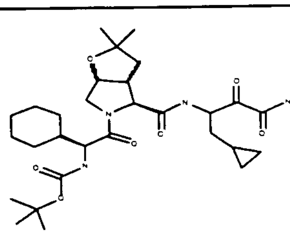
	543	C
	574	A
	534	C
	549	B
	562	A
	662	A
	563	B

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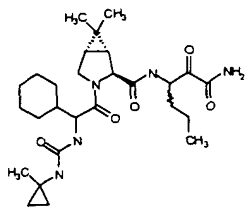
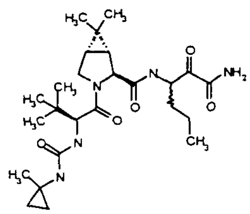
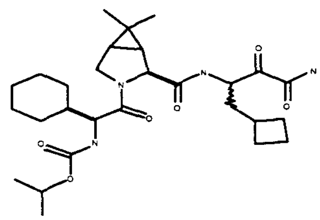
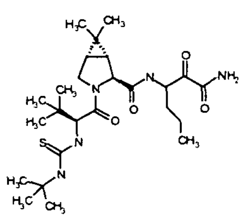
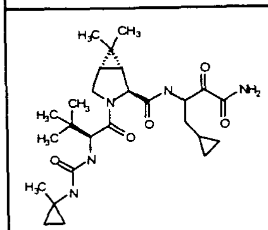
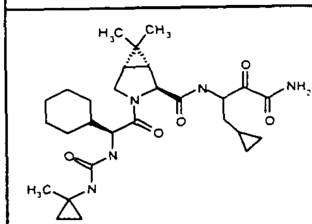
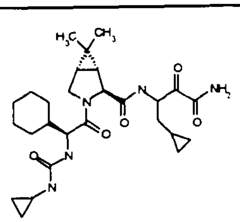
	518	B
	492	B
	533	A
	510	C
	504	A
	530	B
	516	B

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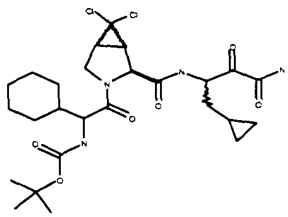
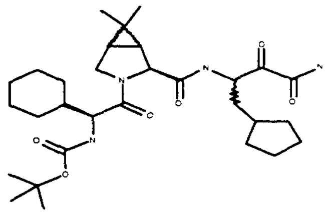
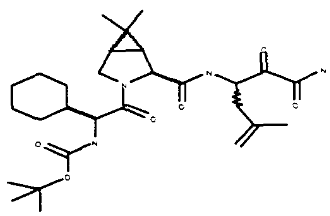
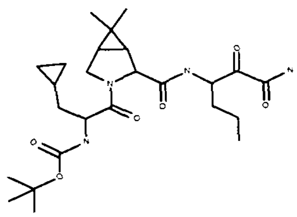
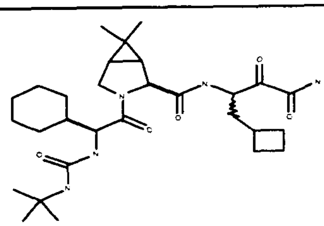
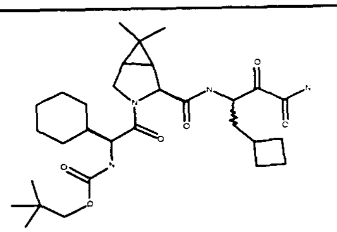
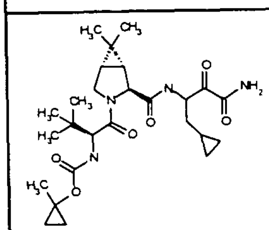
	574	B
	561	B
	533	B
	493	C
	546	A
	561	A
	505	B

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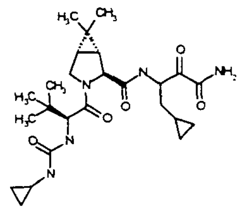
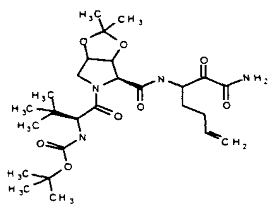
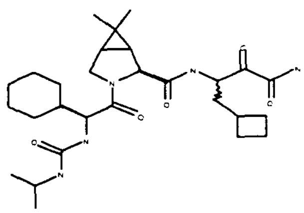
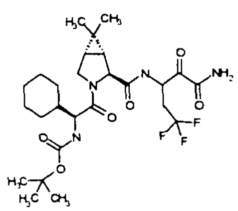
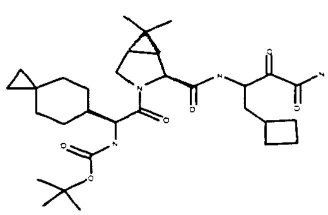
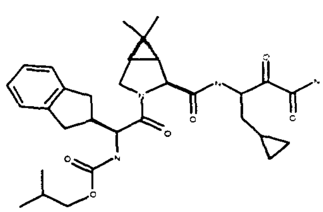
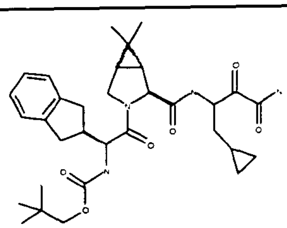
	490	B
	539	C
	532	A
	561	A
	573	A
	567	A
	581	A

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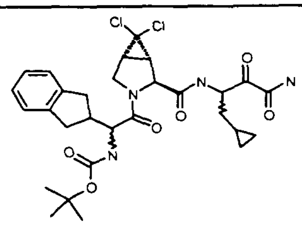
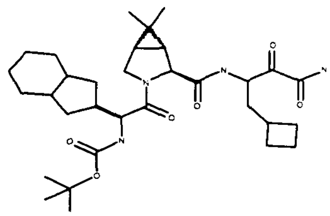
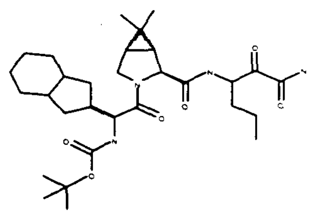
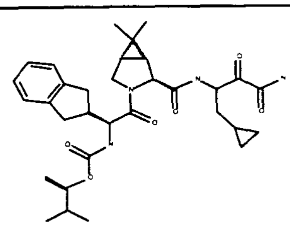
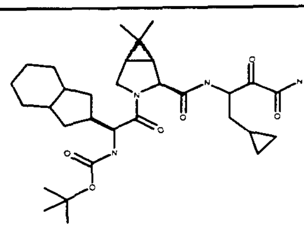
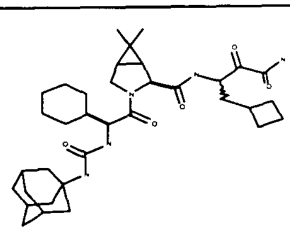
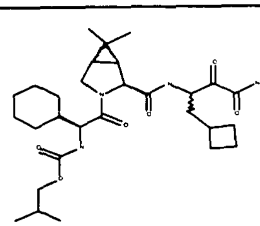
	608	A
	587	B
	561	B
	581	A
	573	A
	624	A
	547	A

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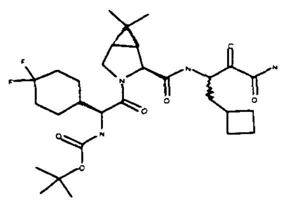
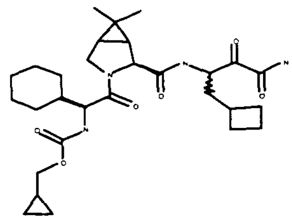
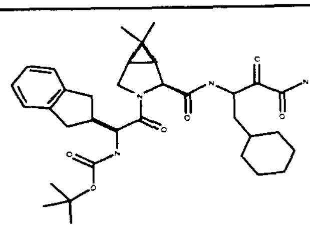
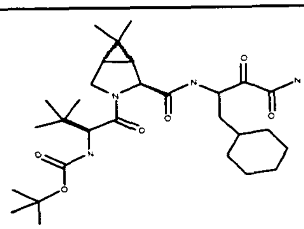
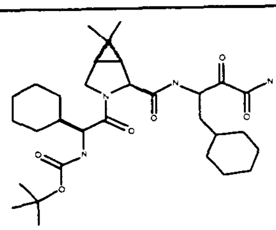
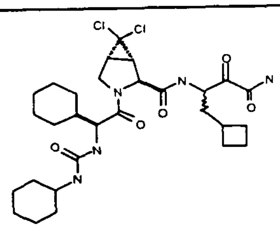
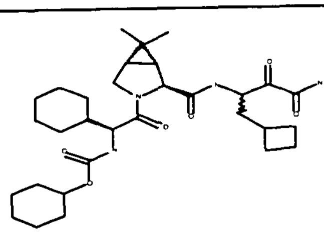
	583	A
	545	B
	609	C
	549	C
	575	C
	613	A
	573	A

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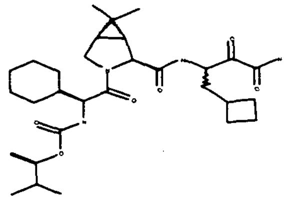
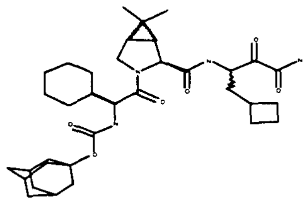
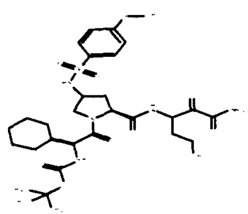
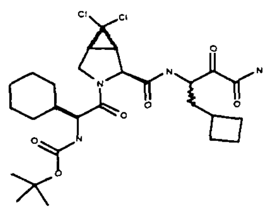
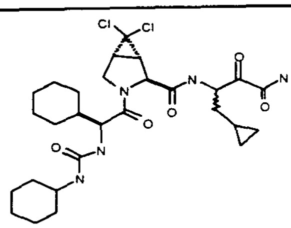
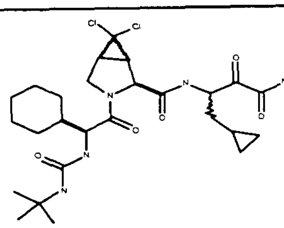
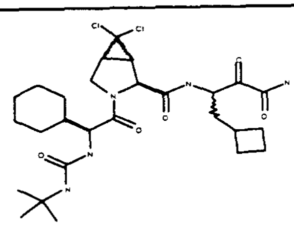
	561	A
	625	A
	666	C
	588	A
	599	A
	573	A
	587	A

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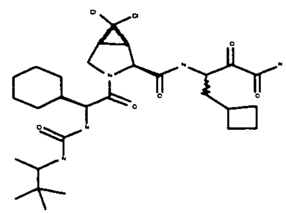
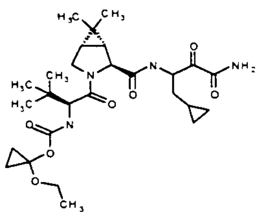
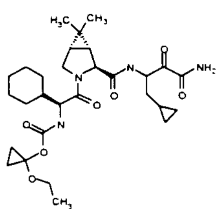
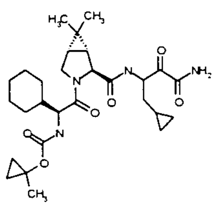
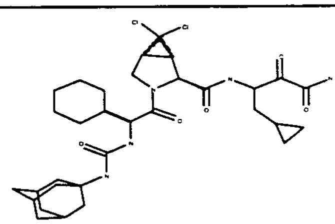
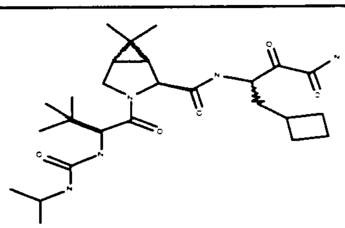
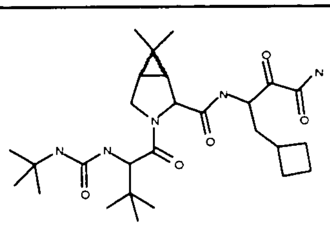
	615	A
	535	B
	561	A
	531	A
	651	A
	506	A
	520	A

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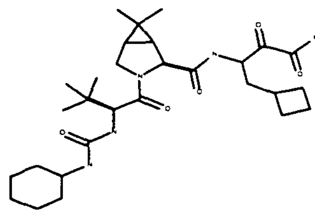
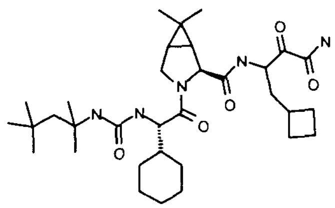
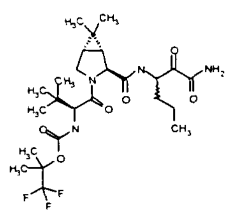
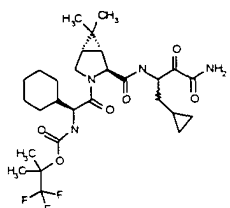
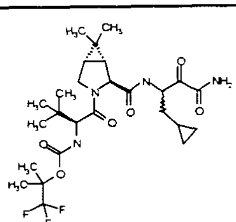
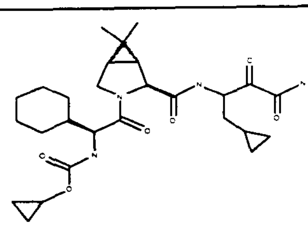
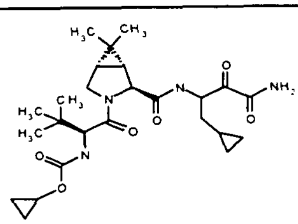
	546	A
	602	A
	549	B
	587	A
	561	A
	517	B
	491	B

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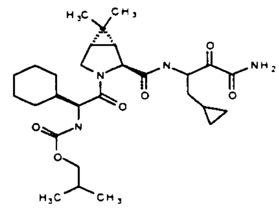
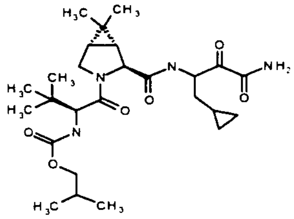
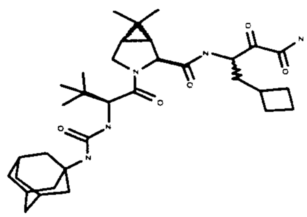
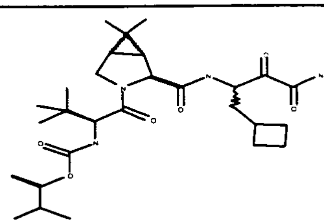
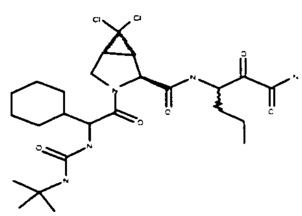
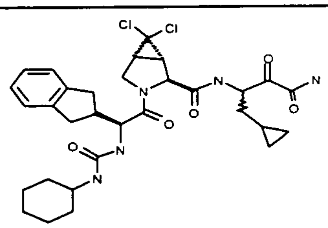
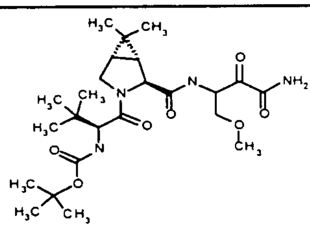
	533	B
	507	A
	598	A
	535	A
	561	A
	633	A
	497	C

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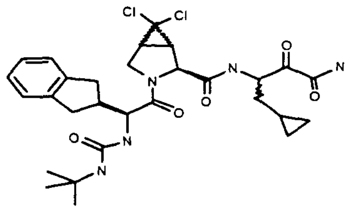
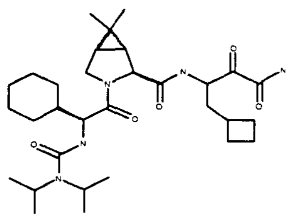
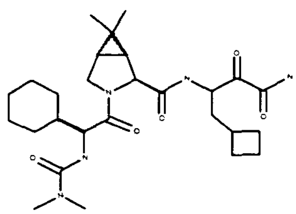
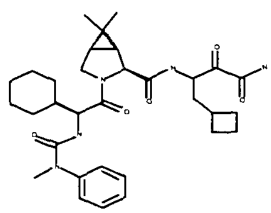
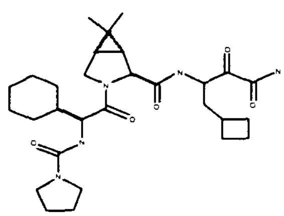
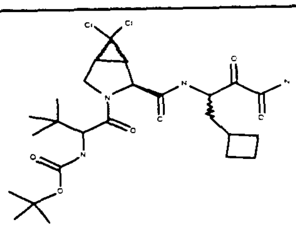
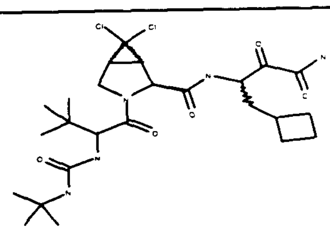
	607	A
	574	B
	518	B
	580	C
	544	B
	562	A
	561	A

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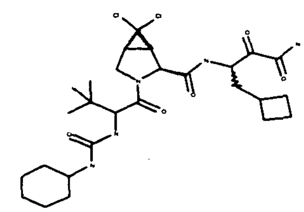
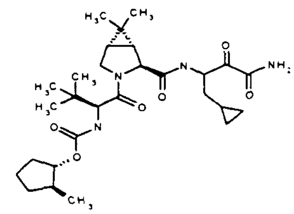
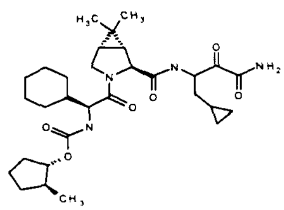
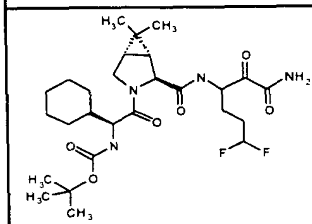
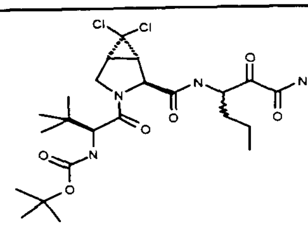
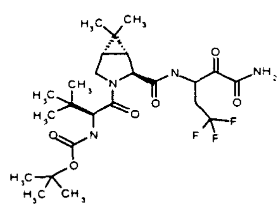
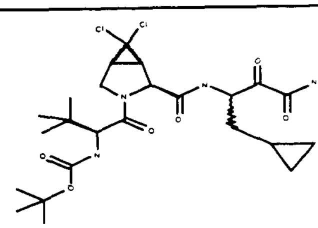
	587	A
	533	A
	559	A
	557	C
	535	A
	535	B
	547	A

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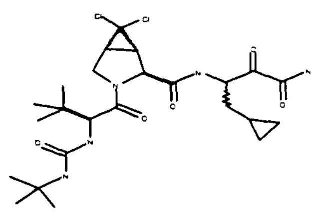
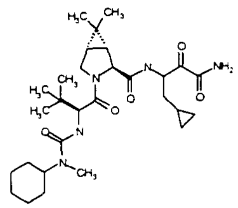
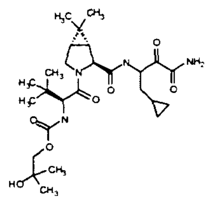
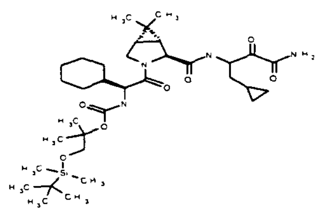
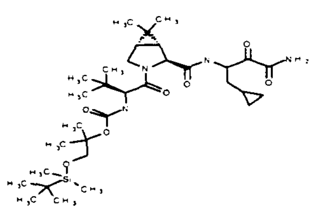
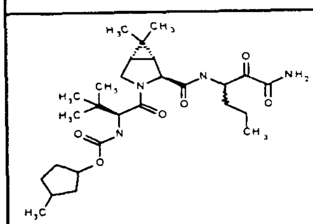
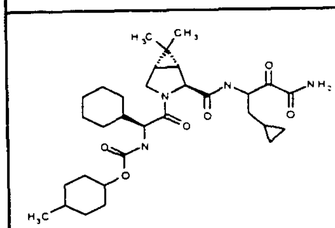
	546	A
	546	B
	523	B
	663	C
	637	C
	521	B
	573	B

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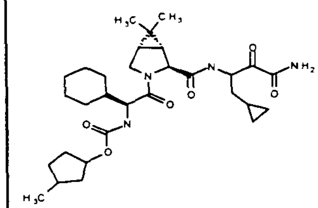
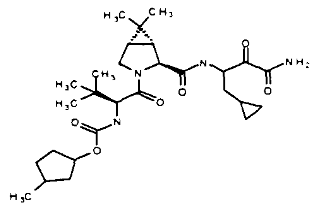
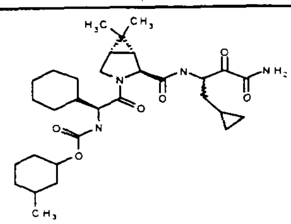
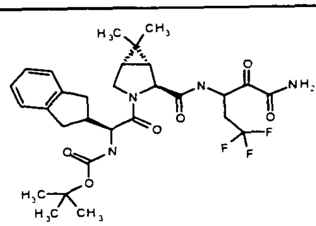
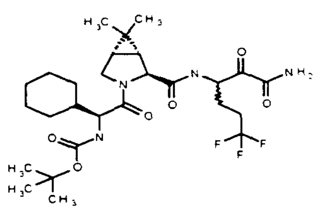
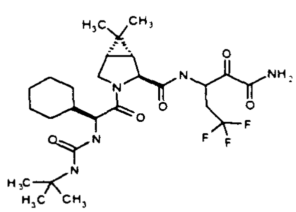
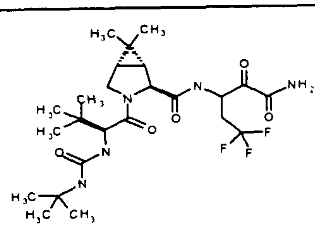
	559	A
	533	A
	573	B
	595	B
	575	A
	560	B
	534	C

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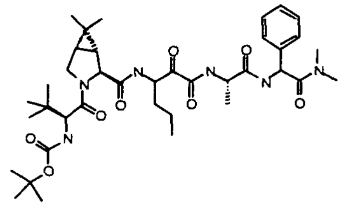
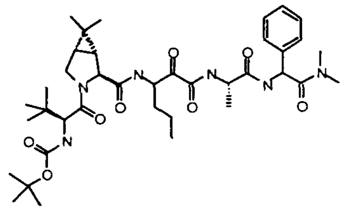
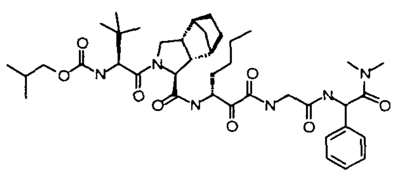
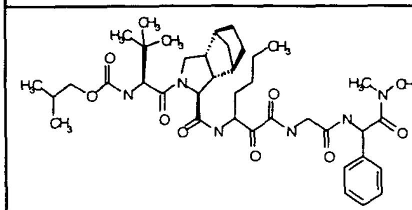
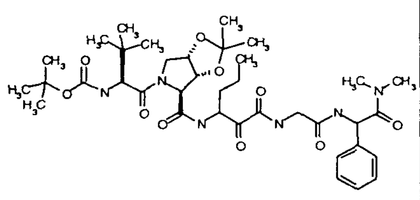
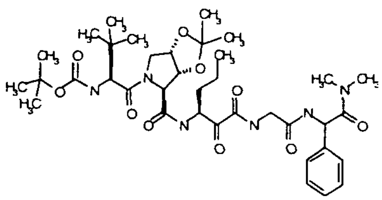
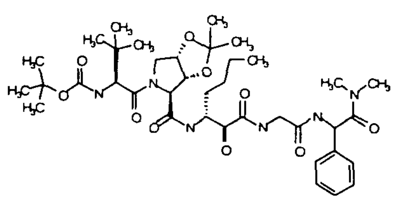
	727	A
	727	A
	753	C
	753	B
	745	A
	745	A
	759	C

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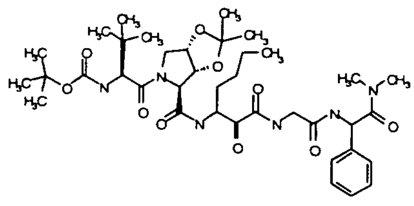
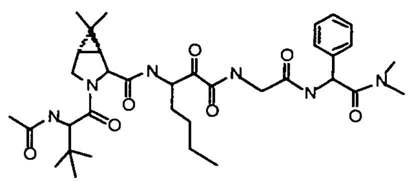
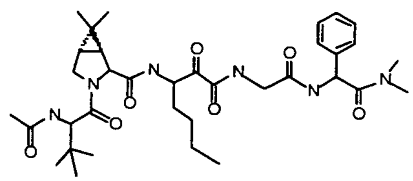
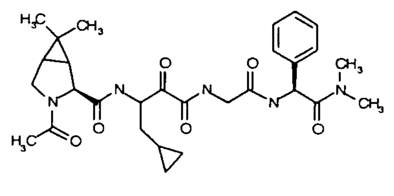
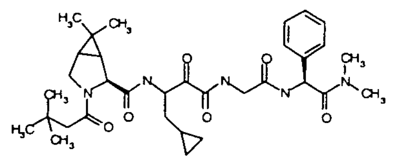
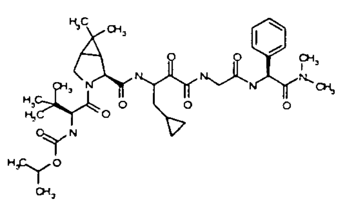
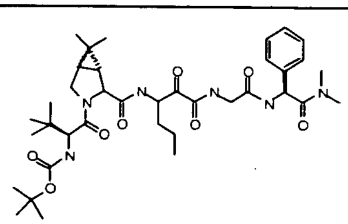
	759	B
	669	B
	669	A
	554	C
	610	B
	711	A
	713	A

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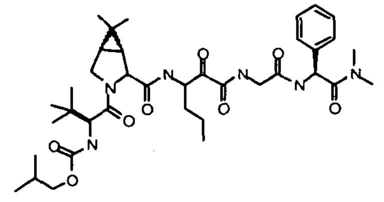
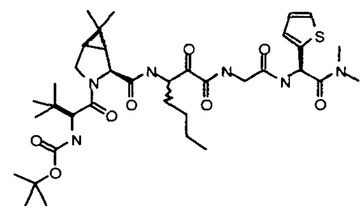
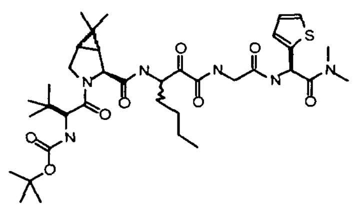
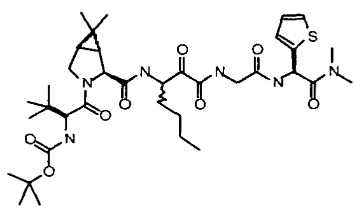
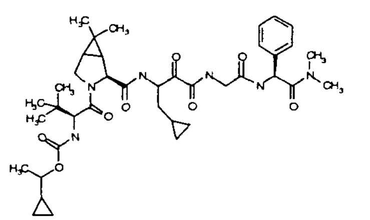
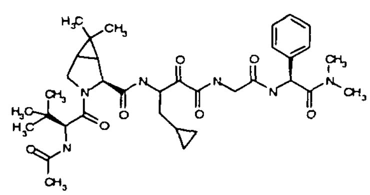
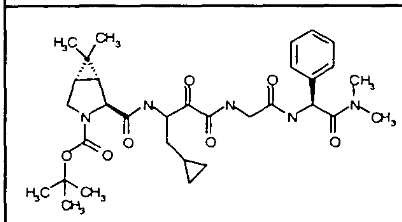
	713	A
	732	A
	733	A
	733	A
	737	A
	667	A
	612	C

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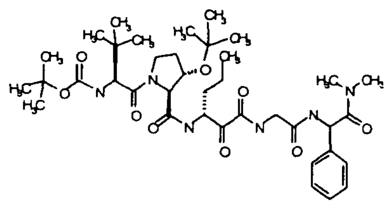
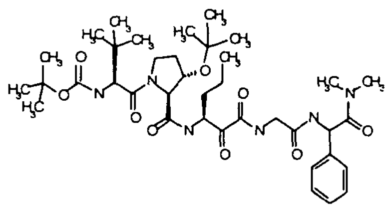
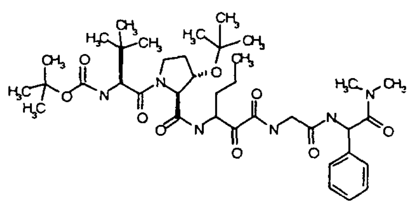
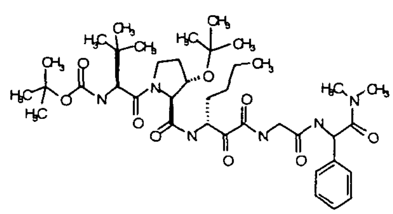
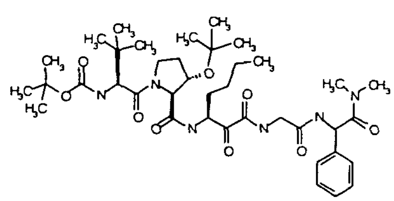
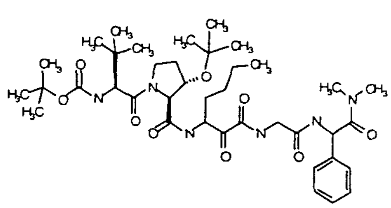
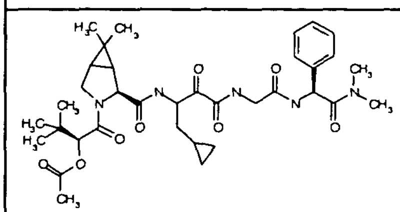
	745	C
	745	C
	745	C
	759	C
	759	C
	759	C
	668	C

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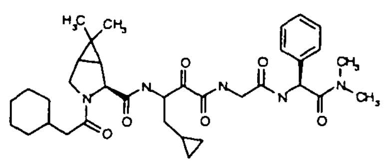
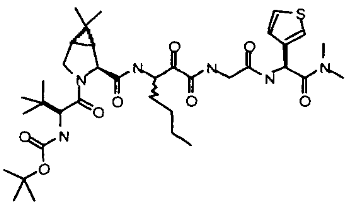
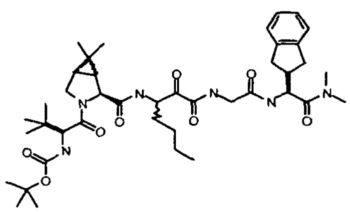
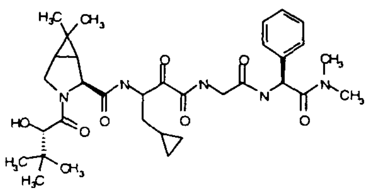
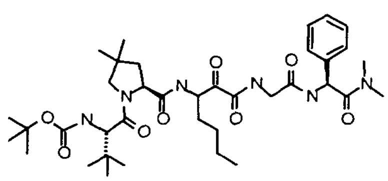
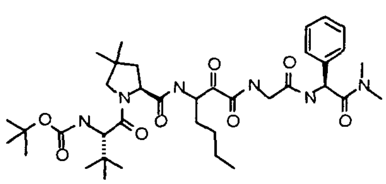
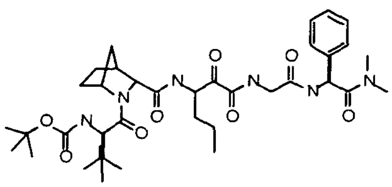
	636	B
	733	A
	767	B
	626	B
	715	C
	715	A
	699	B

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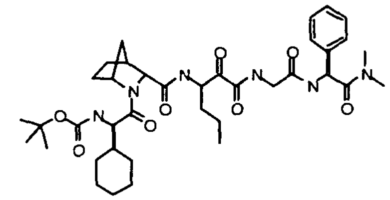
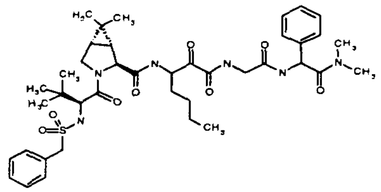
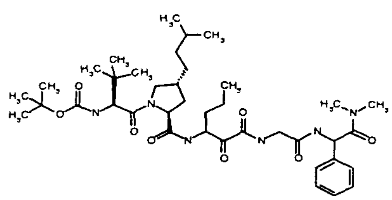
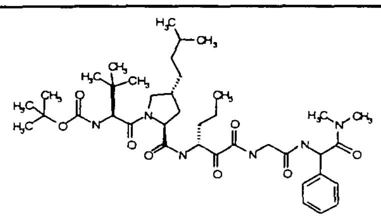
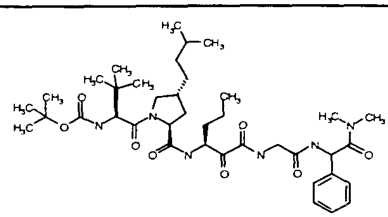
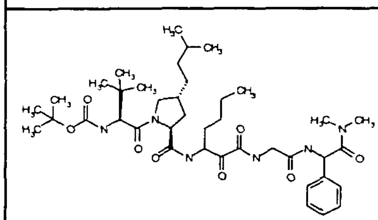
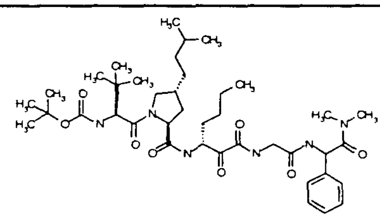
	725	A
	781	B
	743	B
	743	C
	743	A
	757	B
	757	C

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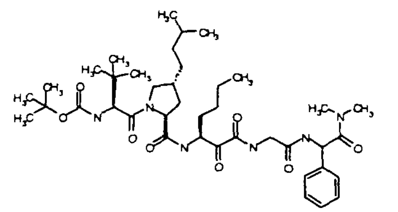
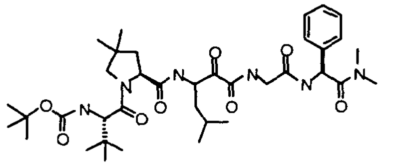
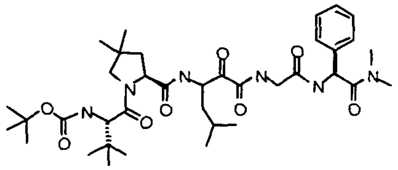
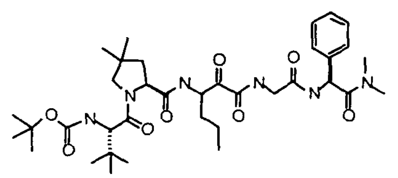
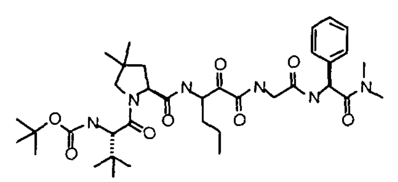
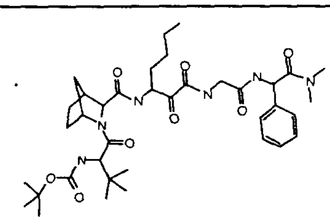
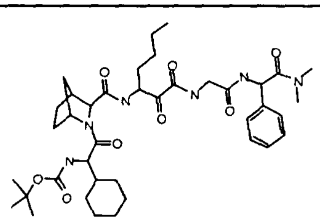
	757	B
	715	A
	715	A
	701	C
	701	A
	713	A
	739	A

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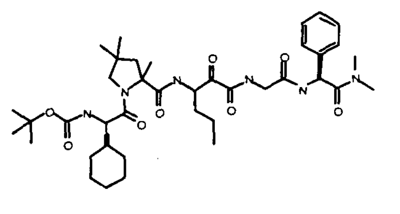
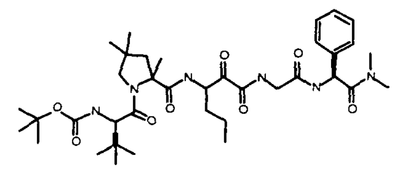
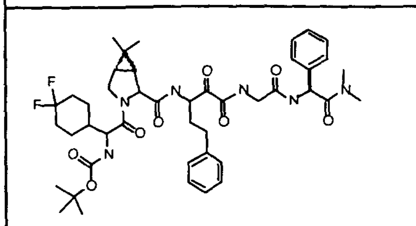
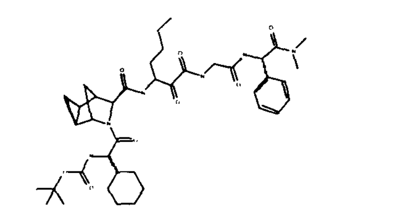
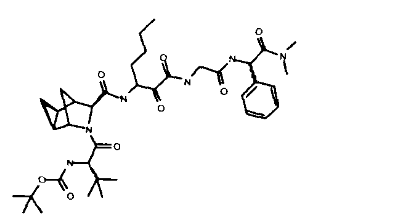
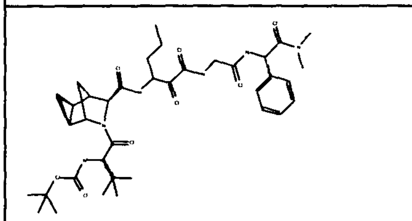
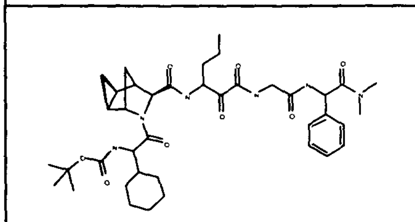
	741	C
	715	C
	837	B
	751	A
	725	C
	711	C
	737	A

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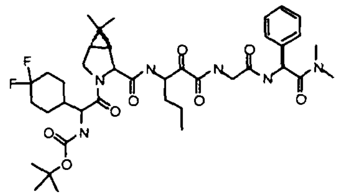
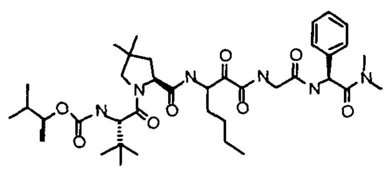
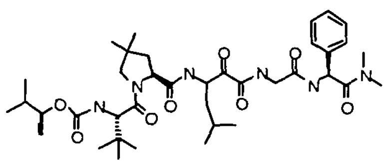
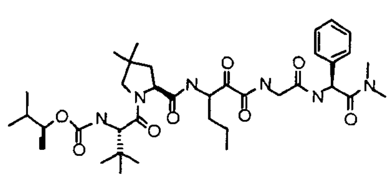
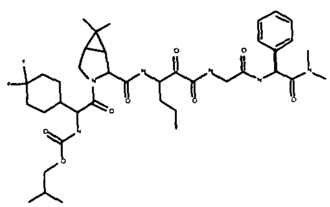
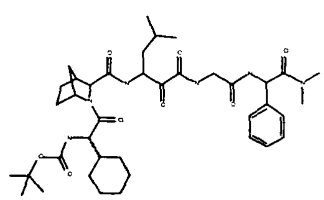
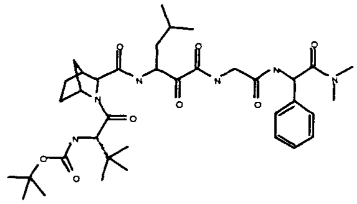
	775	A
	729	A
	729	A
	715	A
	775	A
	739	A
	713	A

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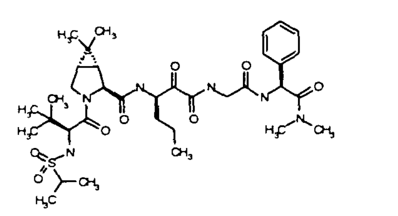
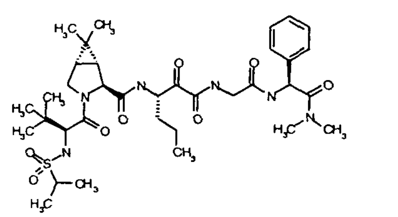
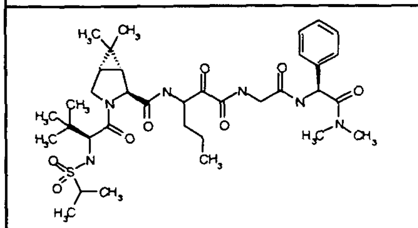
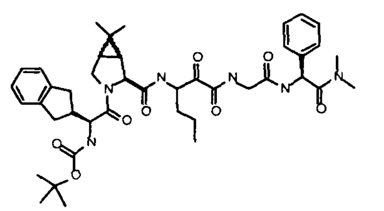
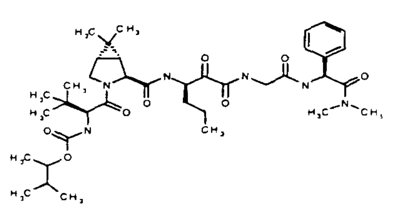
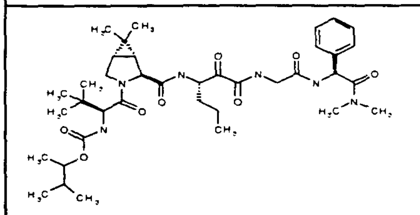
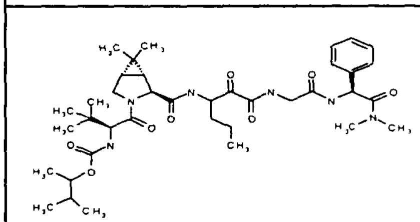
	719	A
	719	A
	719	A
	773	A
	727	A
	727	A
	727	A

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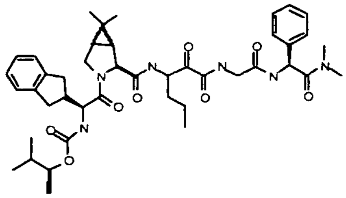
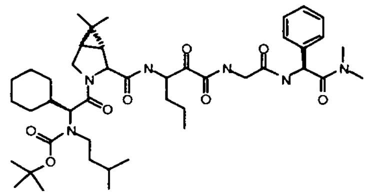
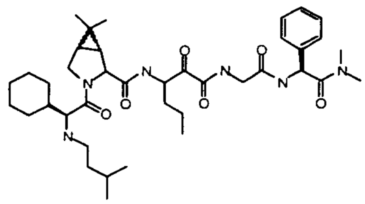
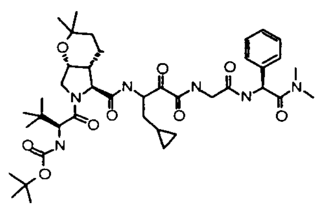
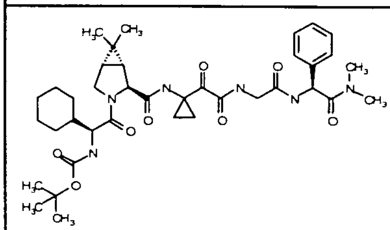
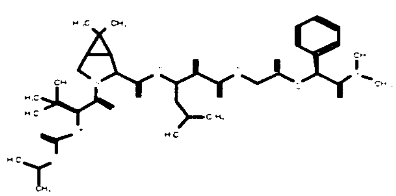
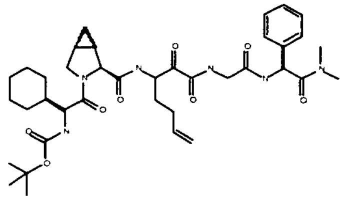
	787	A
	809	C
	709	A
	769	B
	723	C
	713	A
	723	A

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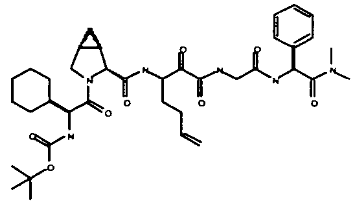
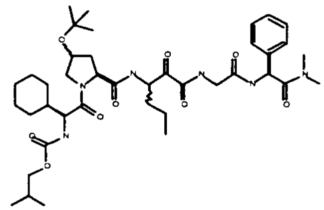
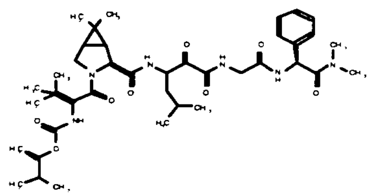
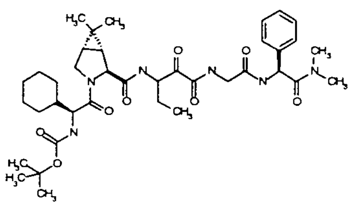
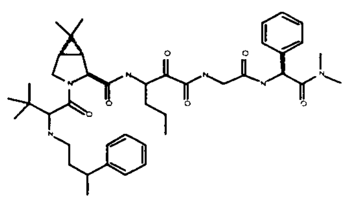
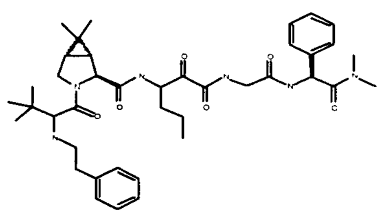
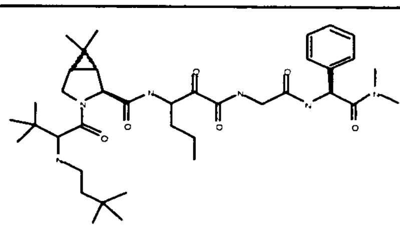
	723	B
	771	C
	741	A
	725	A
	745	A
	716	A
	733	A

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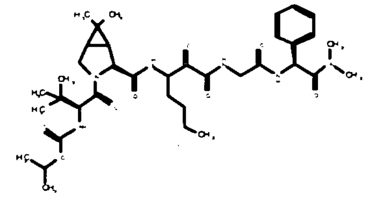
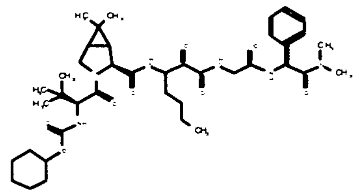
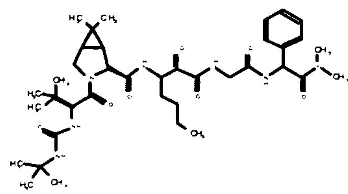
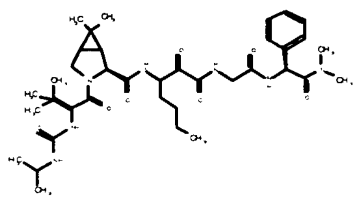
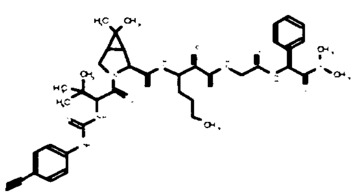
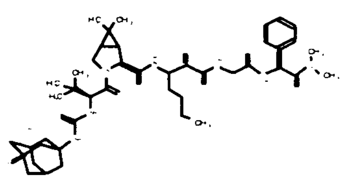
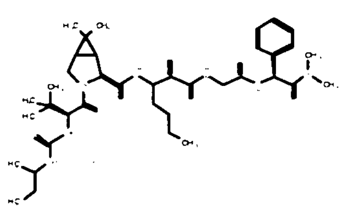
	713	A
	753	A
	726	A
	712	A
	771	B
	804	A
	726	A

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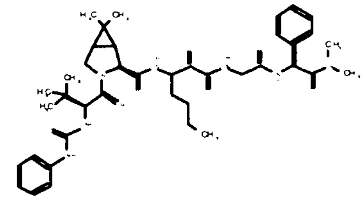
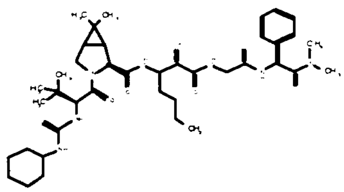
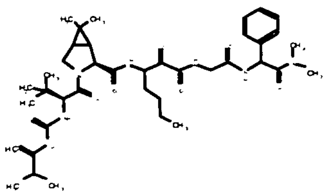
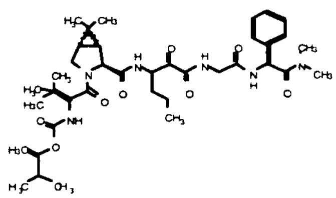
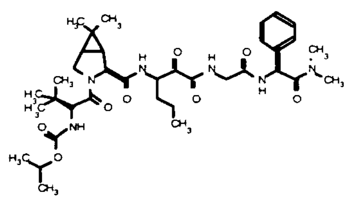
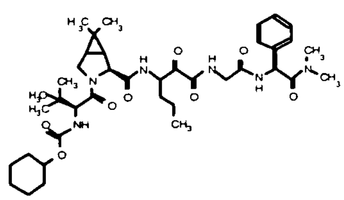
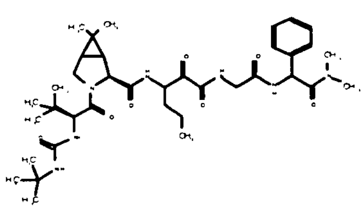
	746	A
	752	A
	741	A
	727	A
	699	A
	739	A
	712	A

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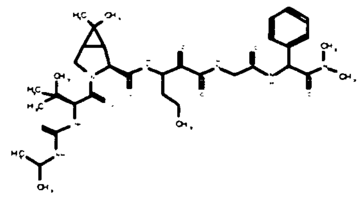
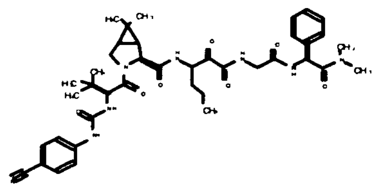
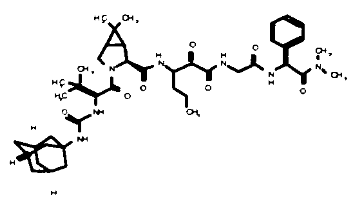
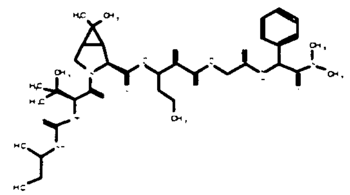
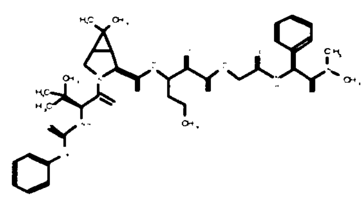
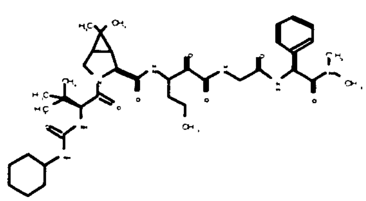
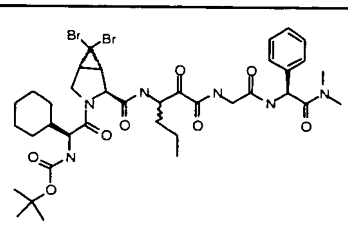
	698	A
	757	B
	790	A
	712	A
	732	A
	738	A
	869	A

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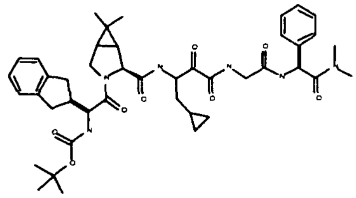
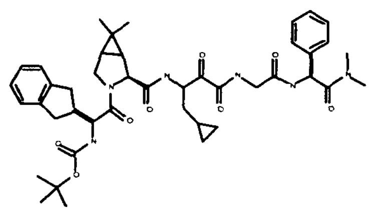
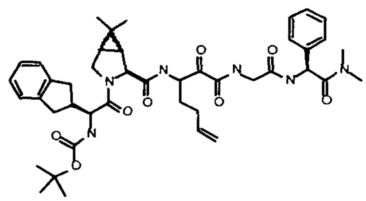
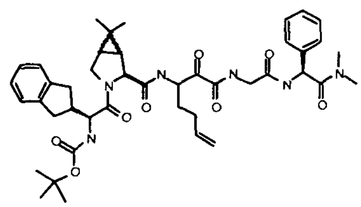
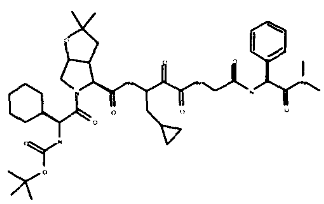
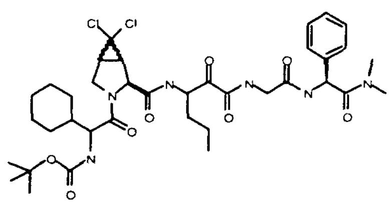
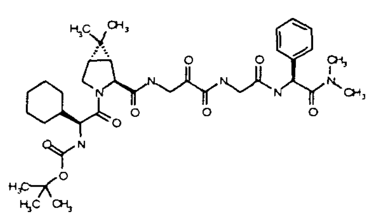
	785	A
	785	A
	785	A
	785	A
	781	A
	780	A
	697	C

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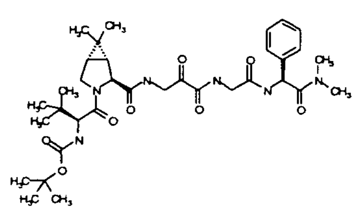
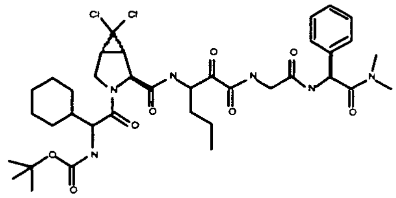
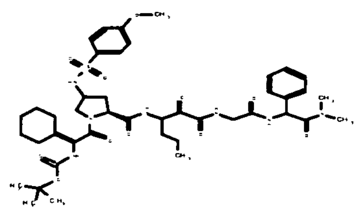
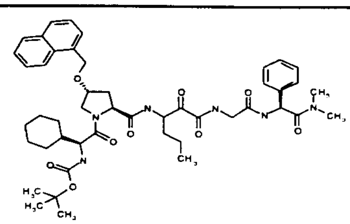
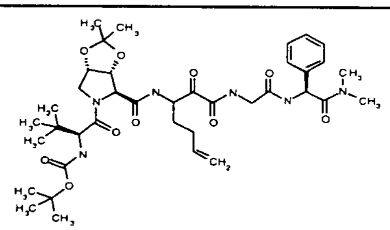
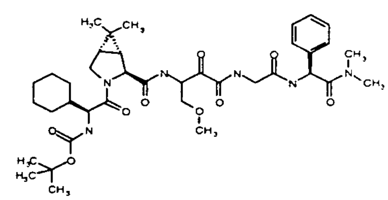
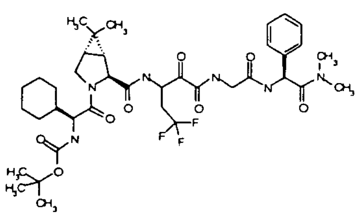
	671	C
	780	A
	884	A
	855	A
	757	B
	741	B
	779	B

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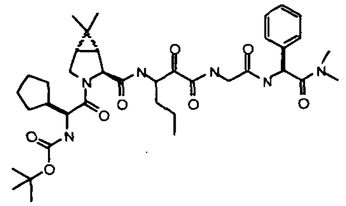
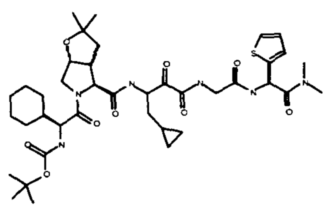
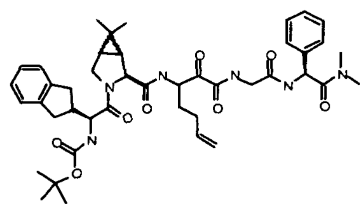
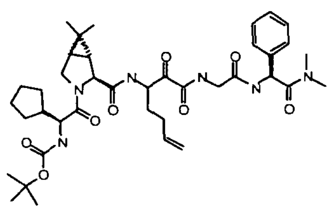
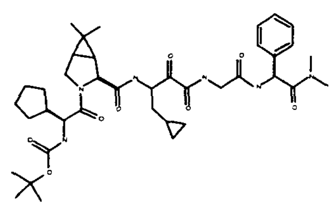
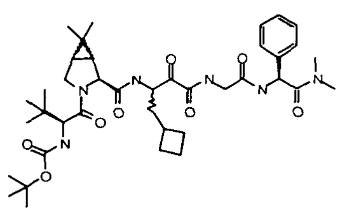
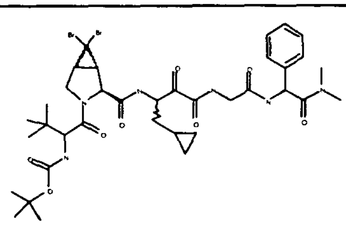
	725	A
	787	A
	785	A
	737	A
	737	A
	739	A
	855	A

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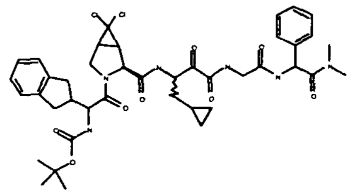
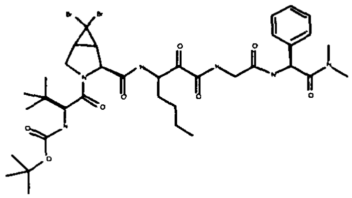
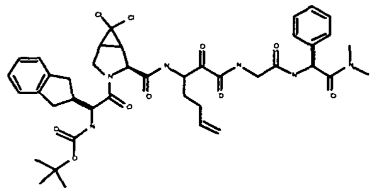
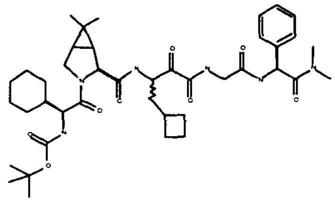
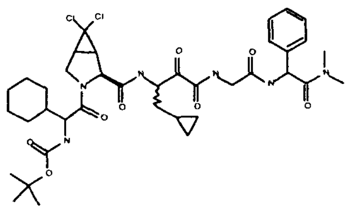
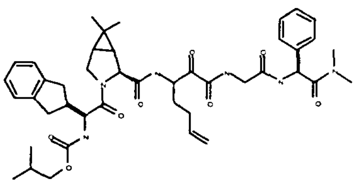
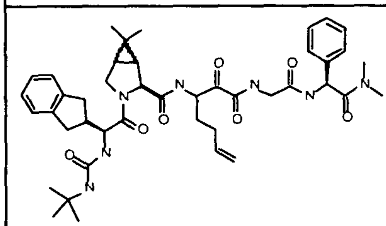
	826	A
	857	A
	826	A
	765	A
	792	A
	799	A
	784	A

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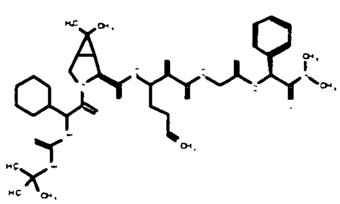
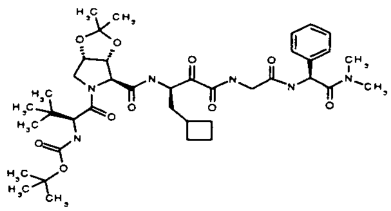
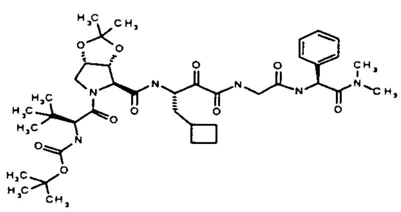
	750	A
	771	A
	771	A

Table 5

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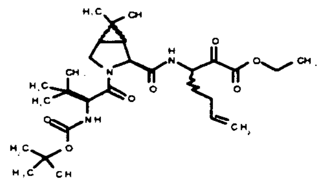
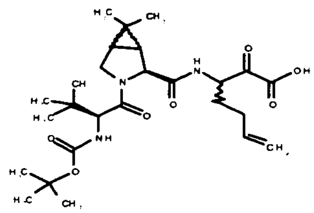
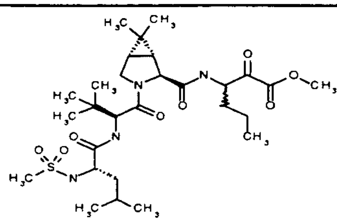
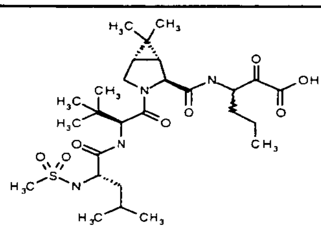
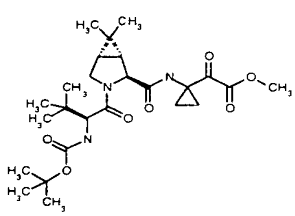
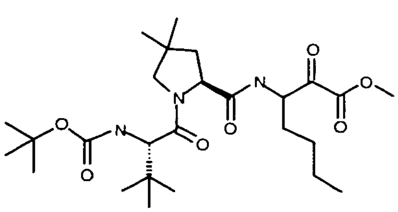
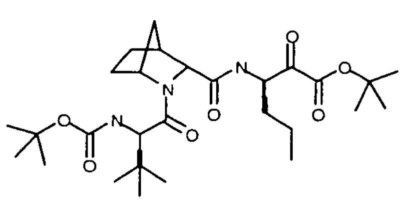
	536	C
	508	B
	601	C
	587	B
	494	C
	512	C
	538	C

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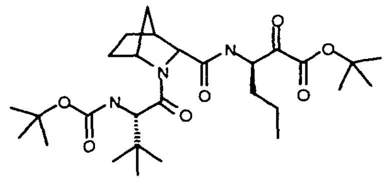
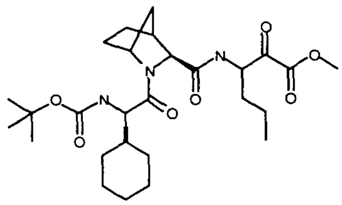
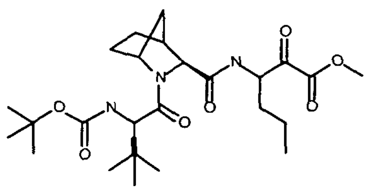
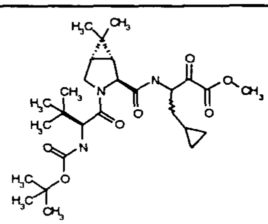
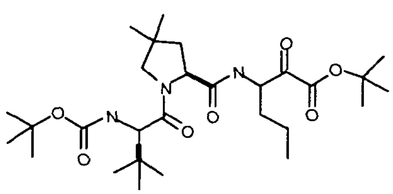
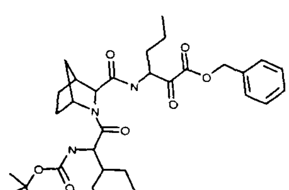
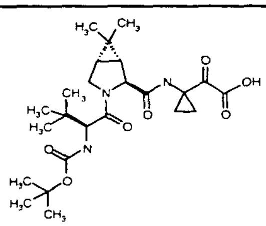
	538	C
	522	C
	496	C
	522	C
	540	C
	598	C
	480	C

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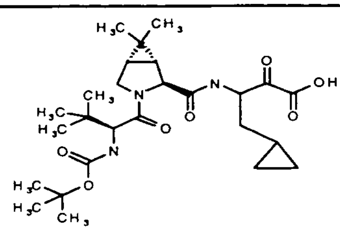
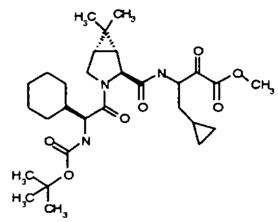
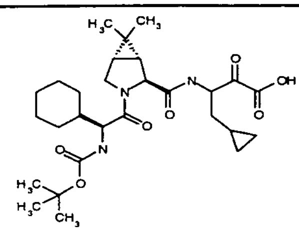
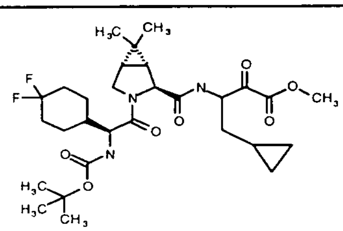
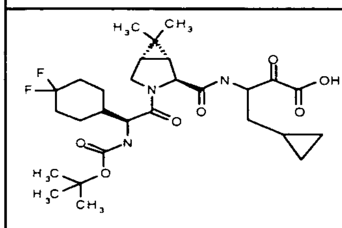
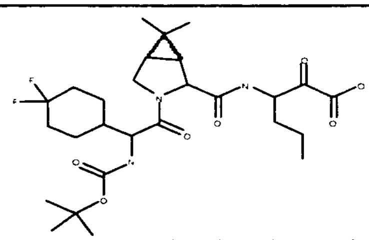
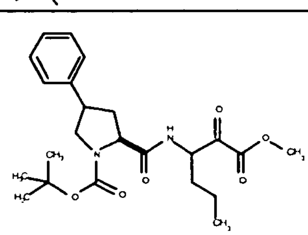
	508	B
	548	C
	534	B
	584	C
	570	B
	558	C
	433	C

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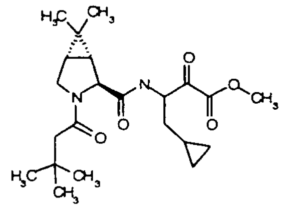
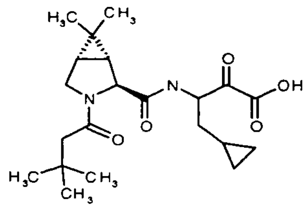
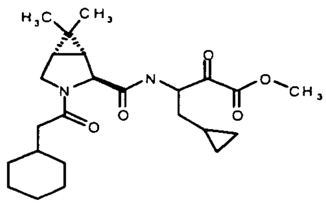
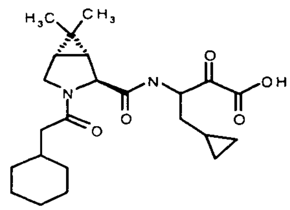
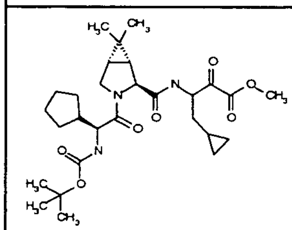
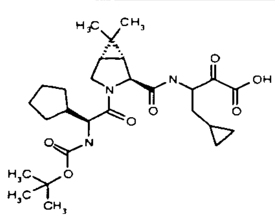
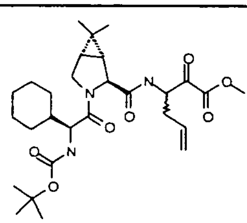
	407	C
	393	C
	433	C
	419	C
	534	C
	520	B
	534	C

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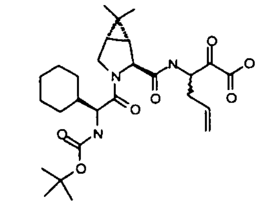
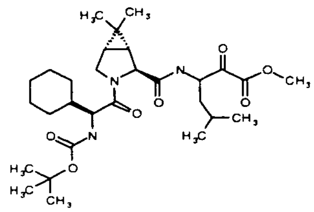
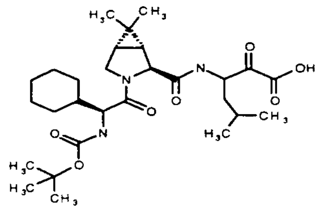
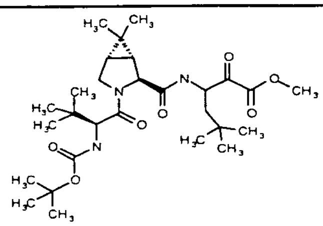
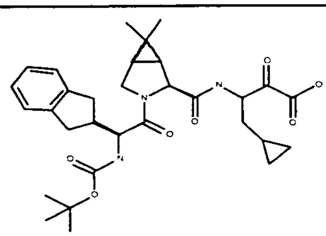
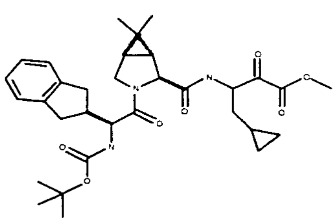
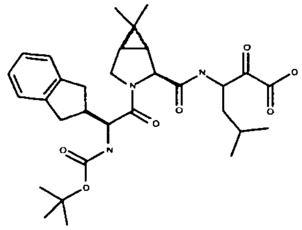
	520	B
	550	C
	536	C
	538	C
	568	B
	582	C
	570	C

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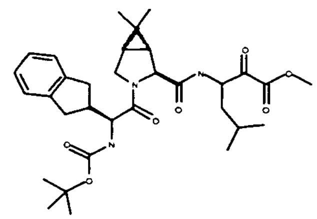
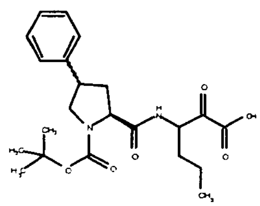
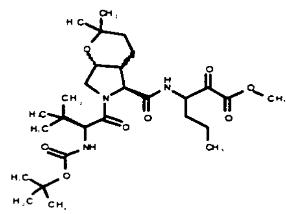
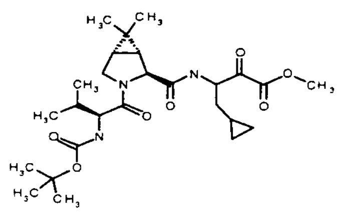
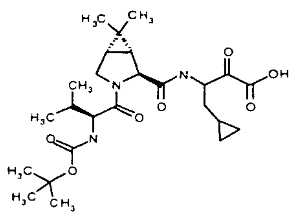
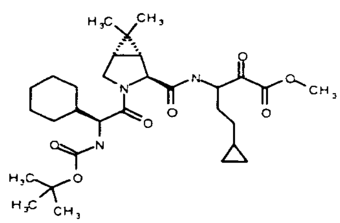
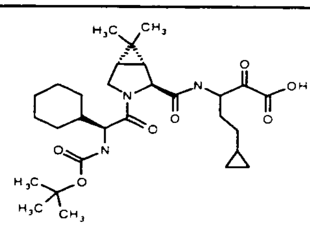
	584	C
	418	C
	554	C
	508	C
	494	B
	562	C
	548	A

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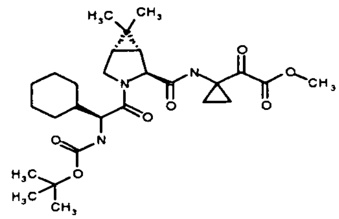
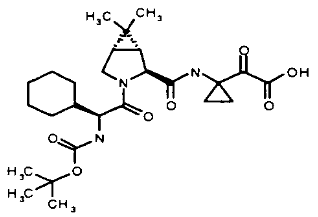
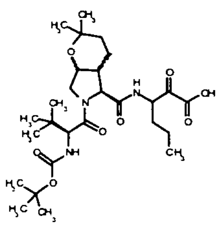
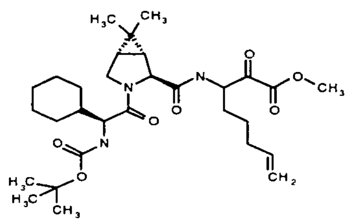
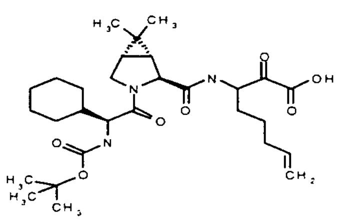
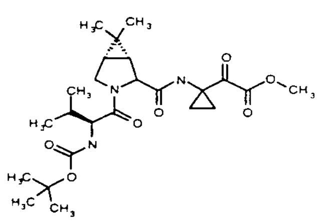
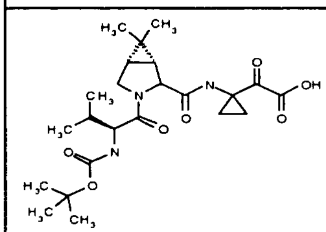
	520	C
	506	C
	540	C
	562	C
	548	B
	480	C
	466	C

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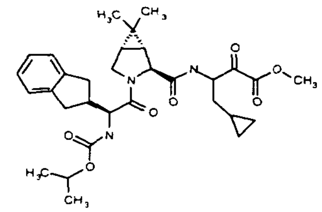
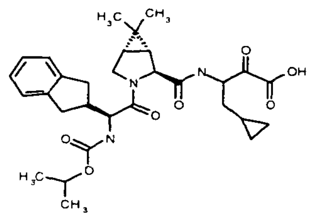
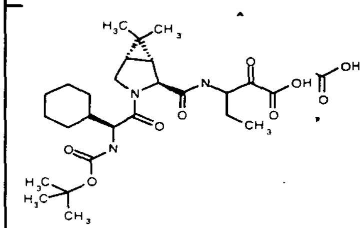
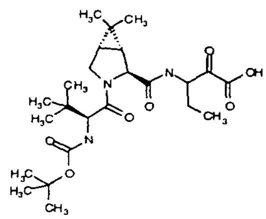
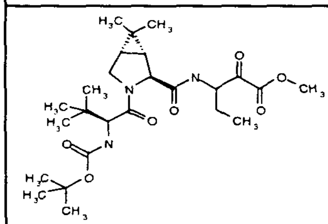
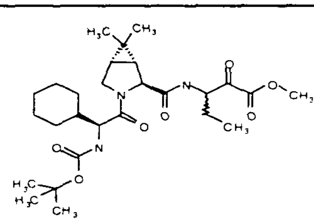
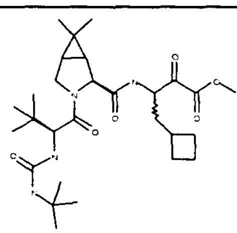
	568	C
	554	B
	508	B
	482	C
	496	C
	522	C
	535	C

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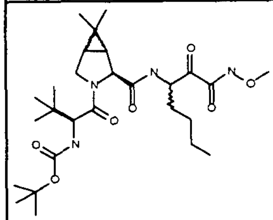
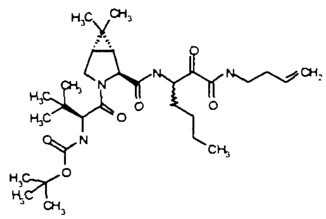
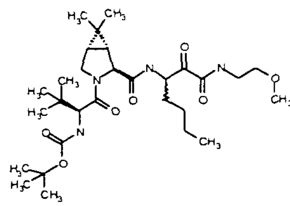
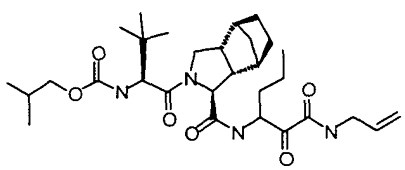
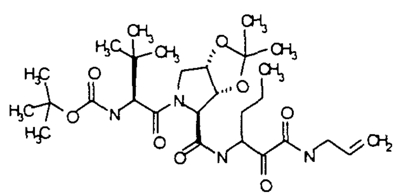
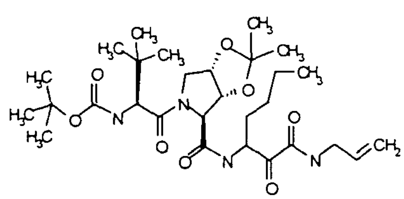
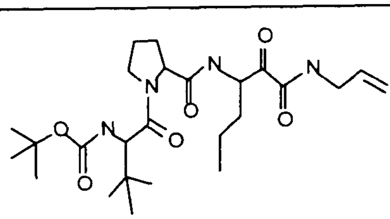
	539	B
	563	B
	567	C
	561	C
	567	C
	581	C
	495	C

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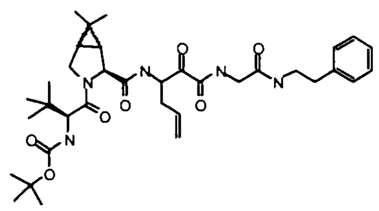
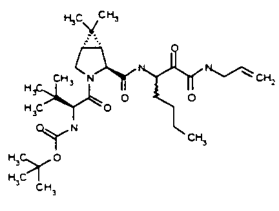
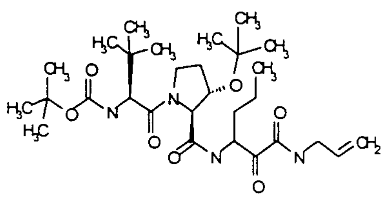
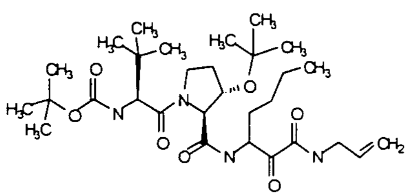
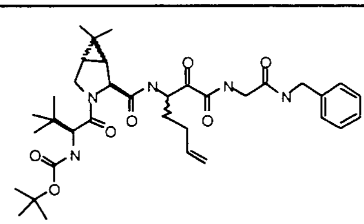
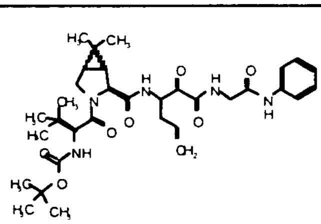
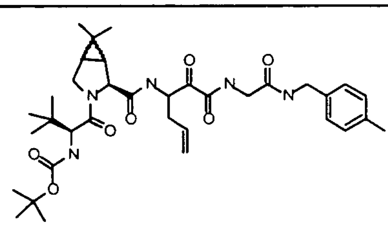
	654	B
	549	C
	567	C
	581	C
	654	C
	626	B
	654	A

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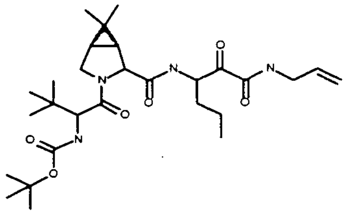
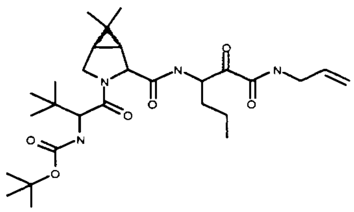
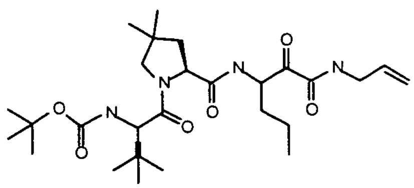
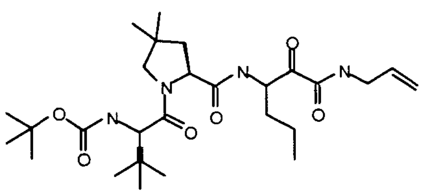
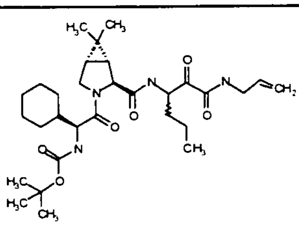
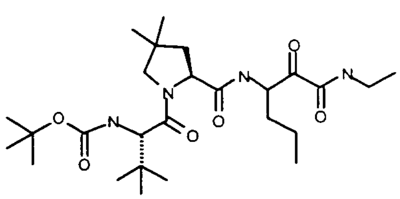
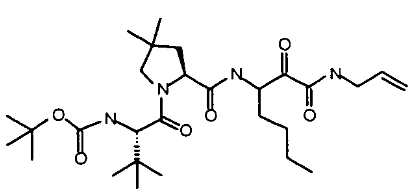
	535	C
	535	B
	523	C
	523	C
	561	B
	511	C
	537	C

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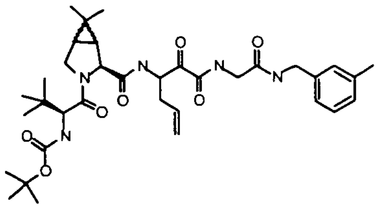
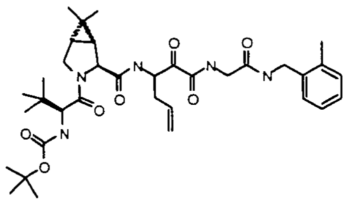
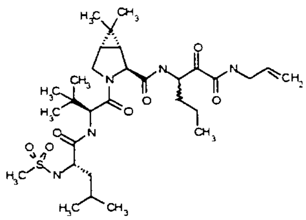
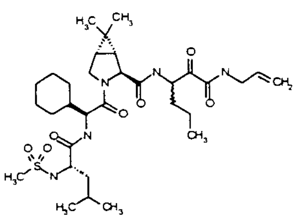
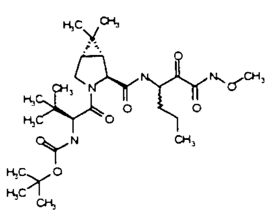
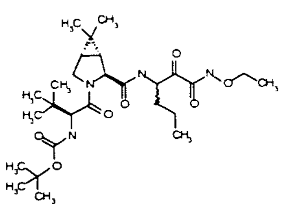
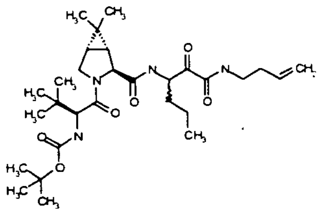
	654	B
	654	A
	626	B
	652	B
	525	C
	539	C
	549	C

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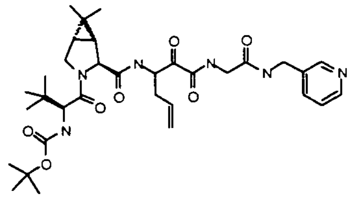
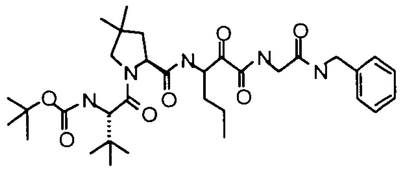
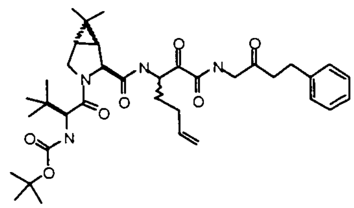
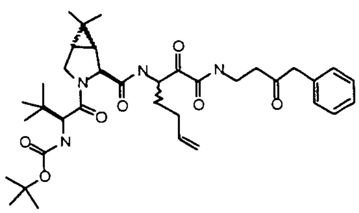
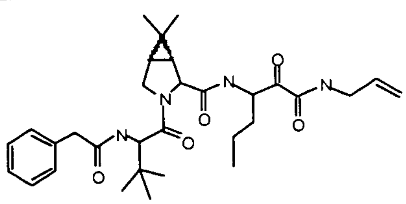
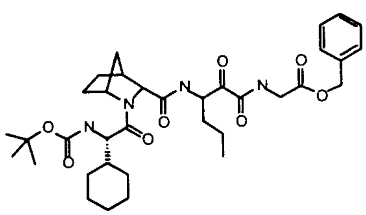
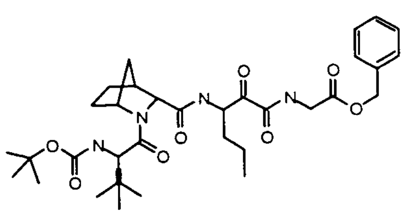
	641	B
	630	C
	653	B
	653	B
	553	C
	655	C
	629	C

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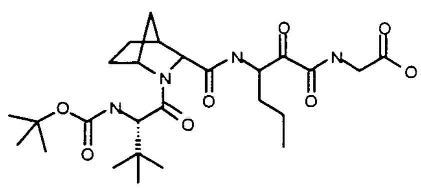
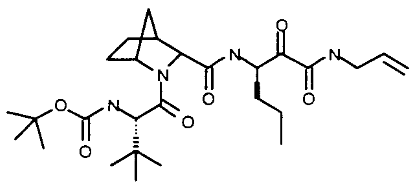
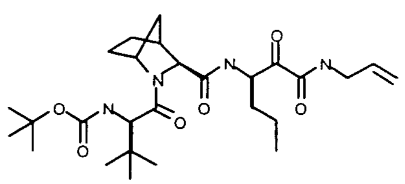
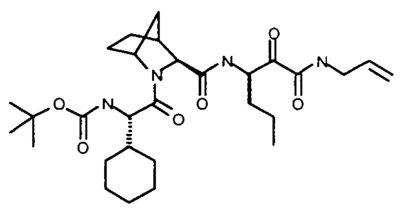
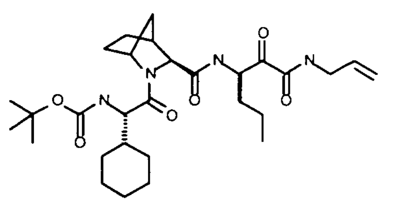
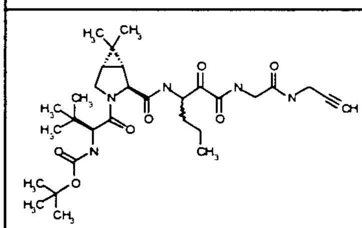
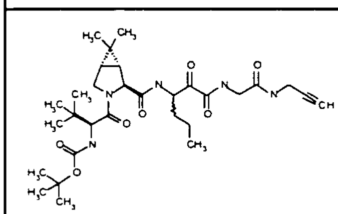
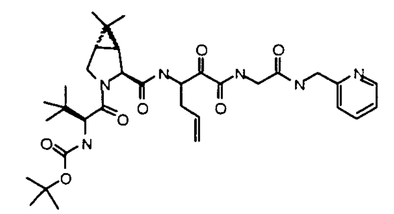
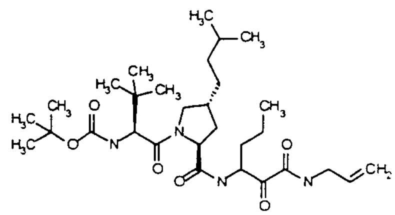
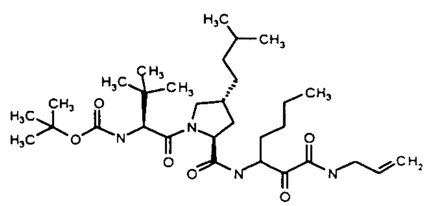
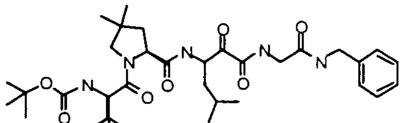
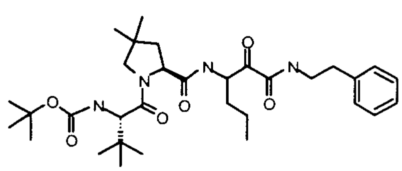
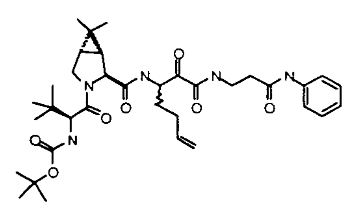
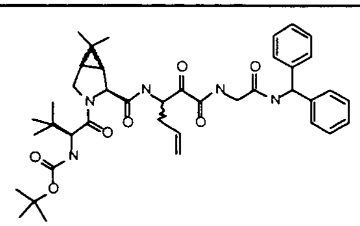
	539	C
	521	C
	521	C
	547	C
	547	C
	590	B
	590	B

	641	B
	565	C
	579	C
	644	C
	587	C
	654	B
	716	B

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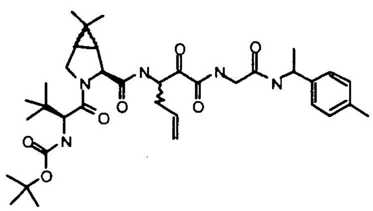
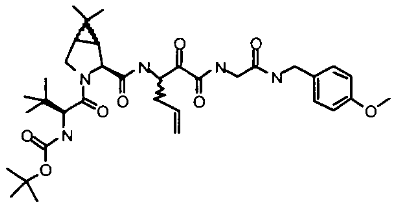
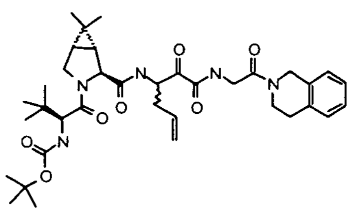
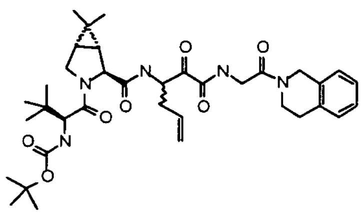
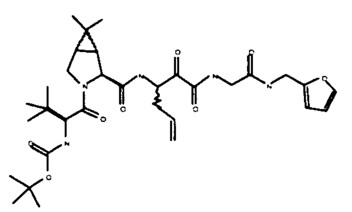
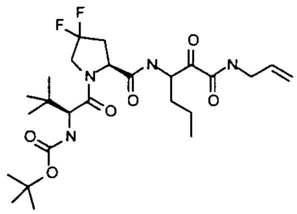
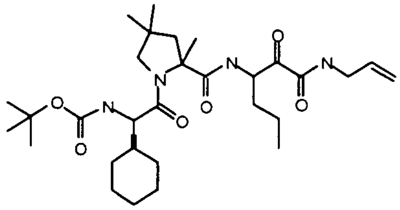
	668	B
	670	A
	666	C
	666	C
	630	B
	531	C
	563	C

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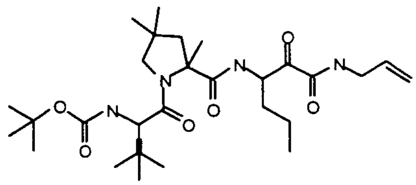
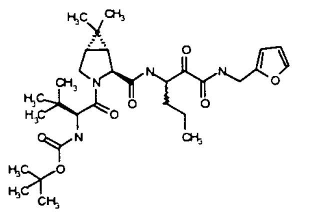
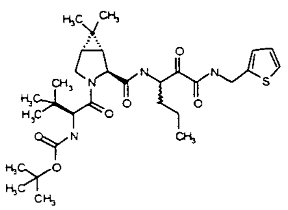
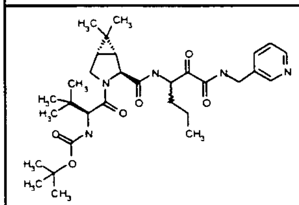
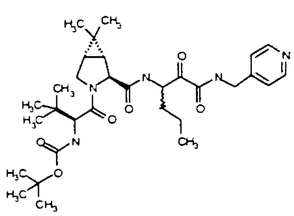
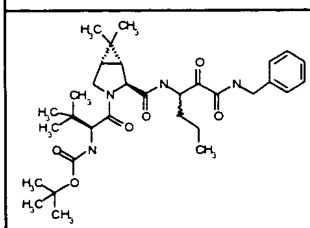
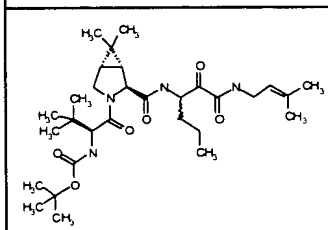
	537	C
	575	B
	591	B
	586	C
	586	C
	585	B
	563	B

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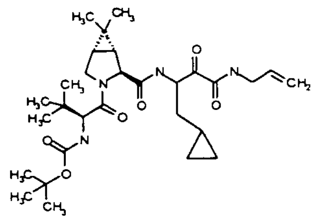
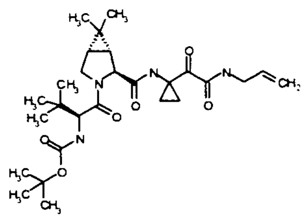
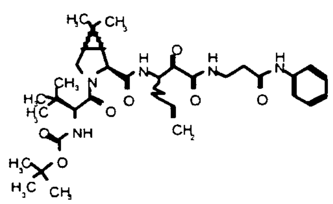
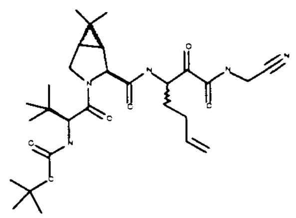
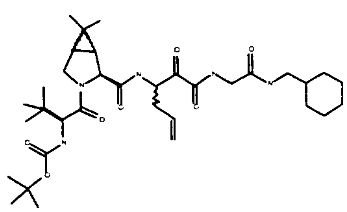
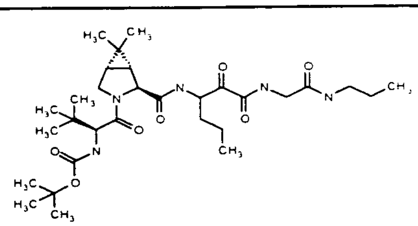
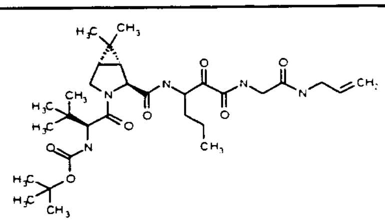
	547	B
	519	C
	640	B
	546	B
	646	B
	594	C
	592	B

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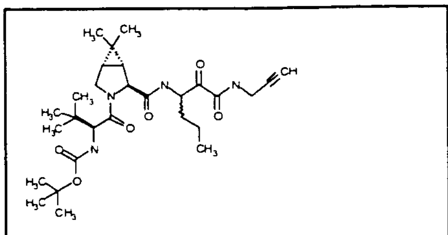
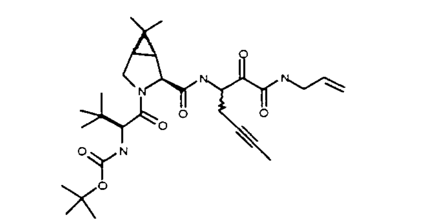
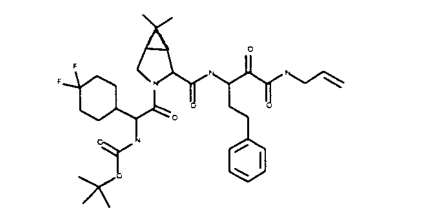
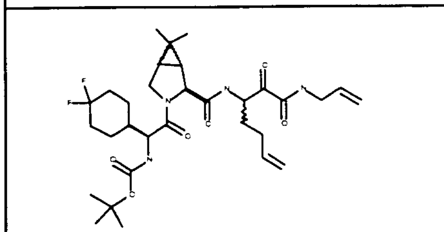
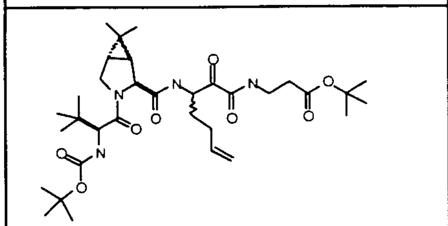
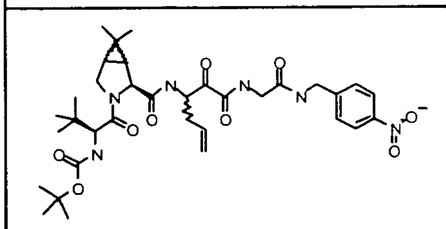
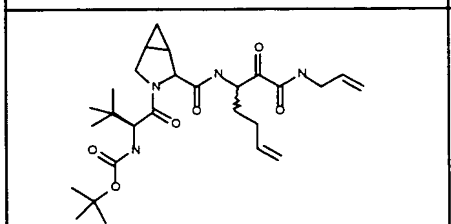
	533	C
	545	C
	659	B
	609	A
	635	B
	685	B
	519	C

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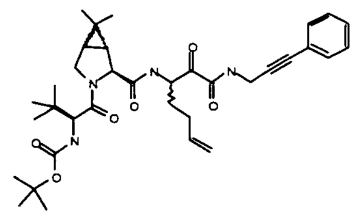
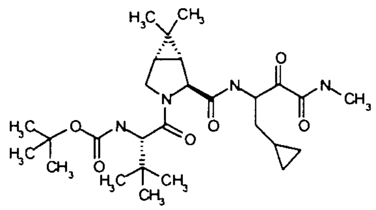
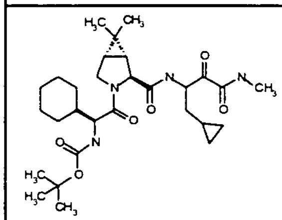
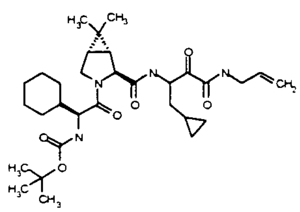
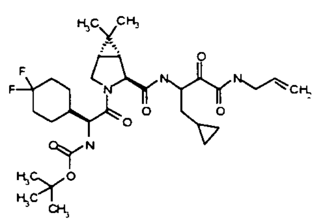
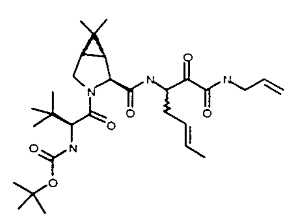
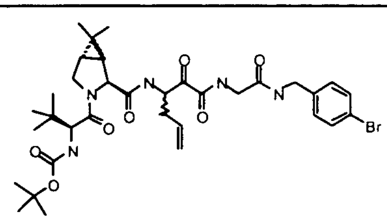
	621	B
	521	B
	547	B
	573	B
	609	B
	547	B
	719	B

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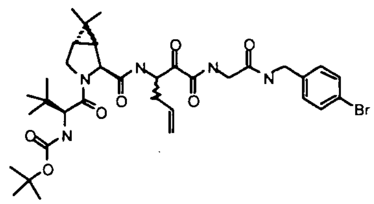
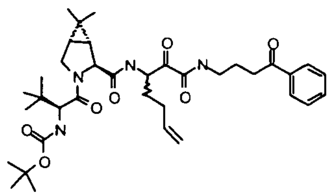
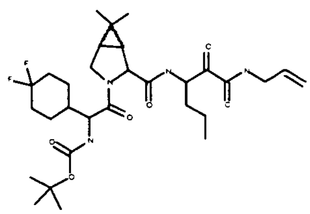
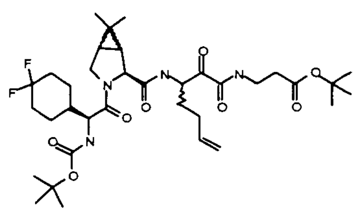
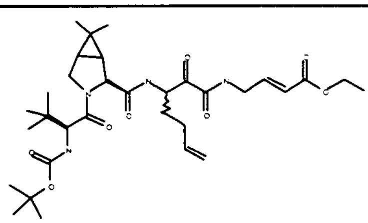
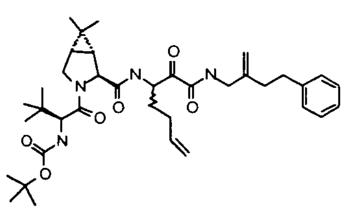
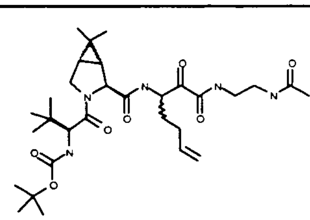
	719	C
	653	B
	597	B
	697	A
	619	B
	651	C
	592	B

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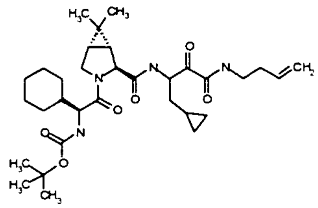
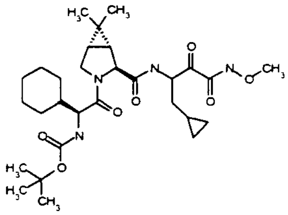
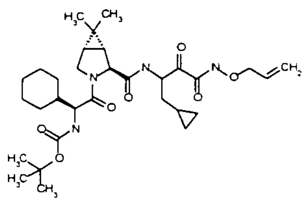
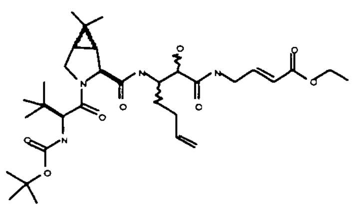
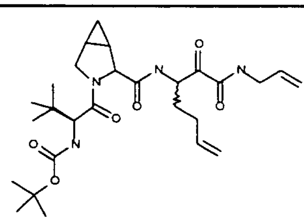
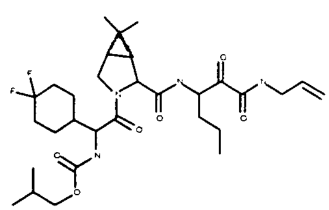
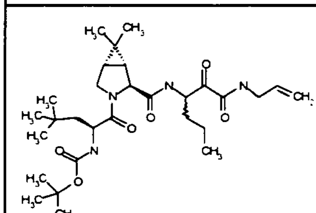
	587	C
	563	B
	589	C
	621	C
	519	C
	597	B
	549	C

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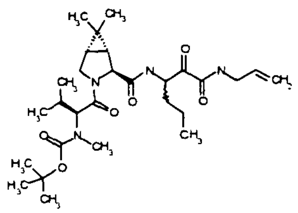
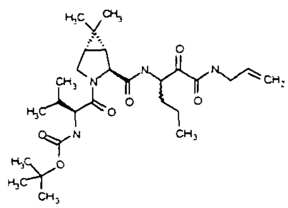
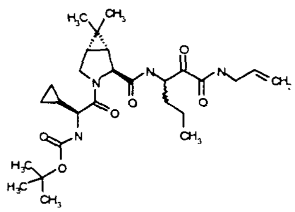
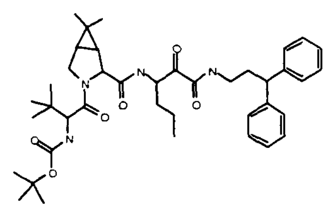
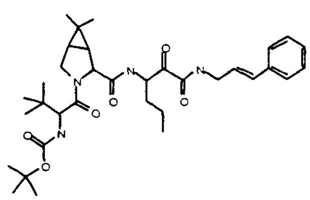
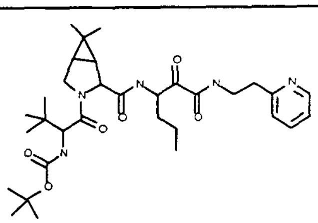
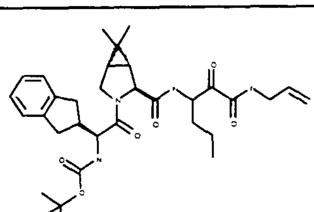
	535	C
	521	B
	519	C
	689	C
	611	C
	600	C
	595	B

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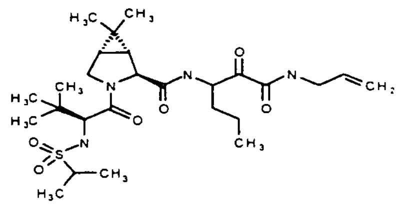
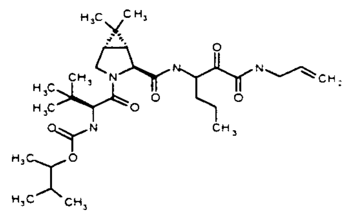
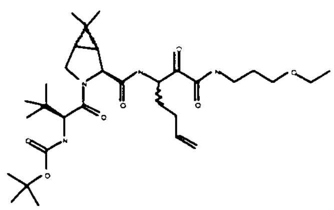
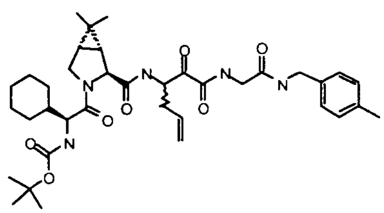
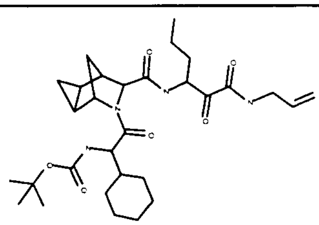
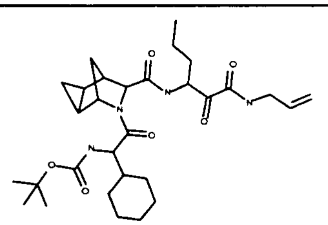
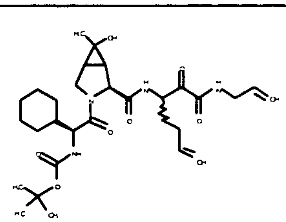
	541	C
	549	B
	593	C
	680	B
	559	C
	559	C
	573	B

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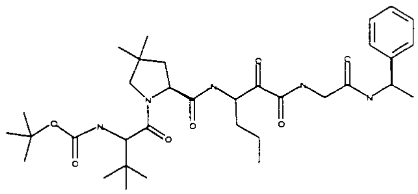
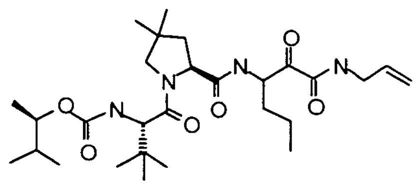
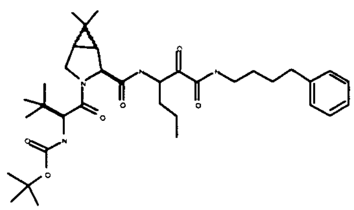
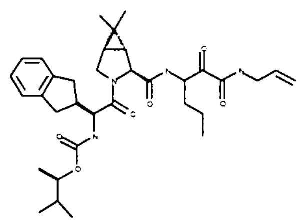
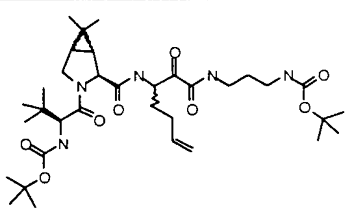
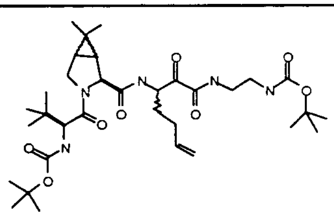
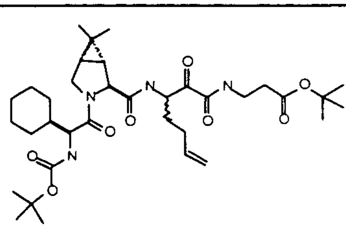
	644	C
	537	C
	627	C
	609	B
	664	B
	650	C
	661	B

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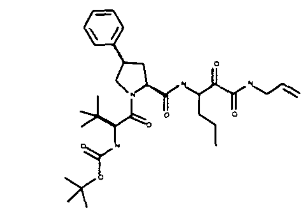
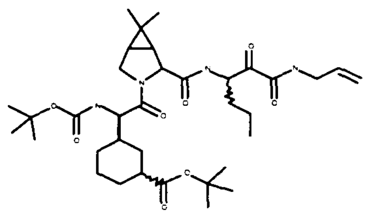
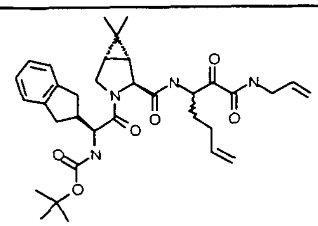
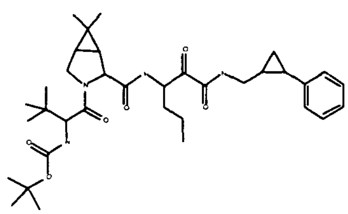
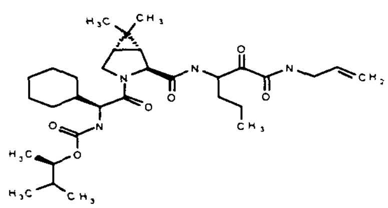
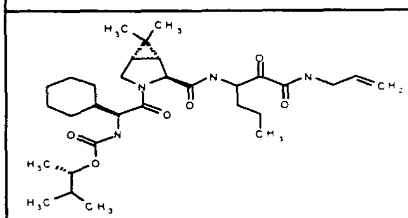
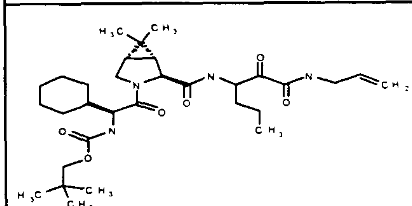
	571	C
	661	B
	607	B
	625	C
	575	B
	575	B
	575	B

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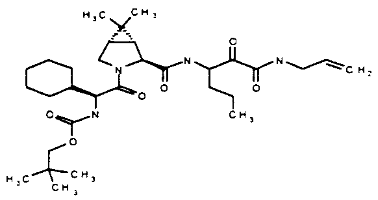
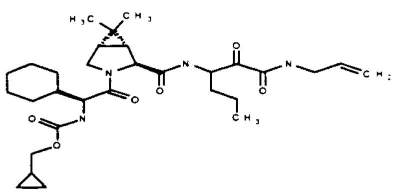
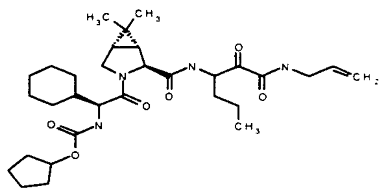
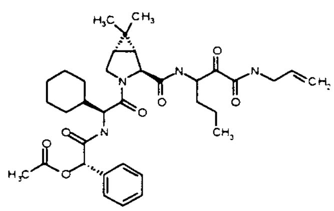
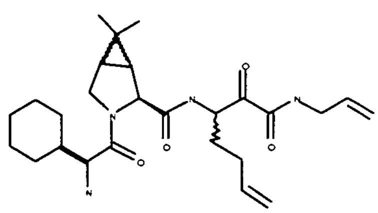
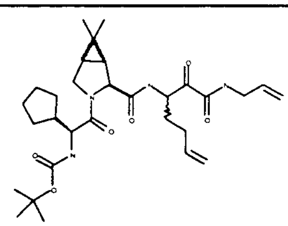
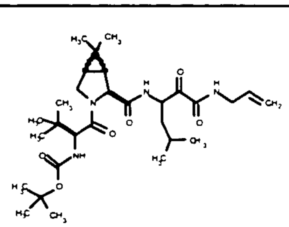
	575	B
	559	B
	573	B
	637	B
	473	C
	559	B
	549	C

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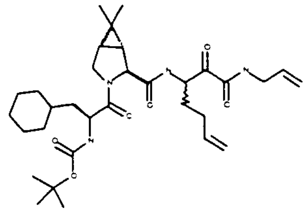
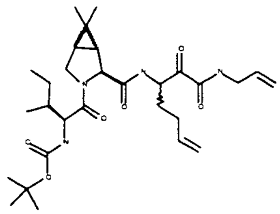
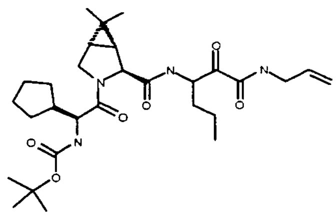
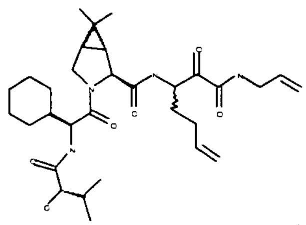
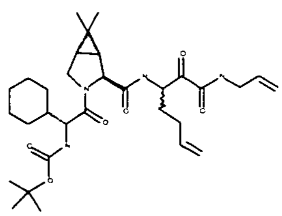
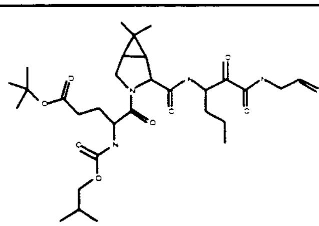
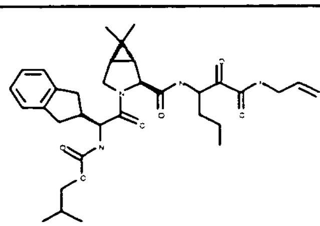
	587	C
	547	C
	547	B
	573	C
	573	C
	607	C
	595	B

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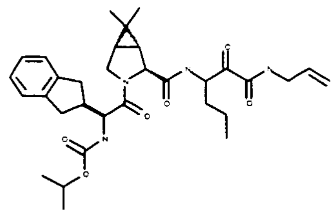
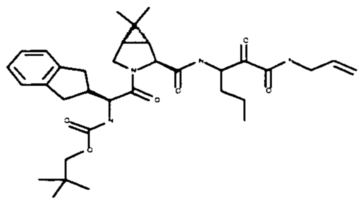
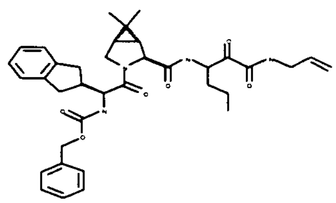
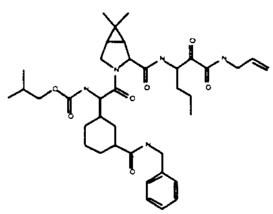
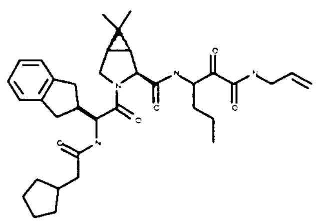
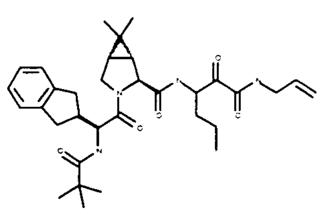
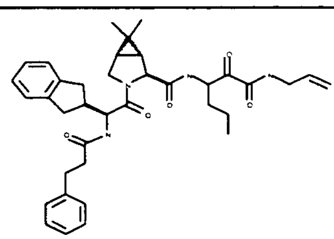
	581	B
	609	B
	629	C
	694	C
	605	C
	579	C
	627	C

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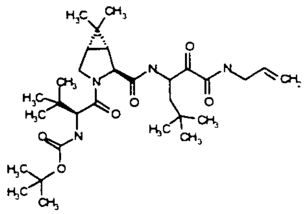
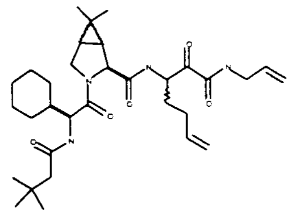
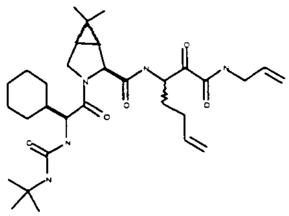
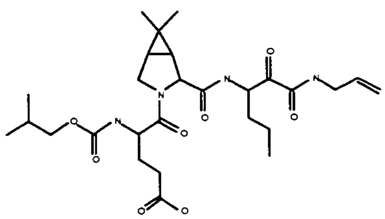
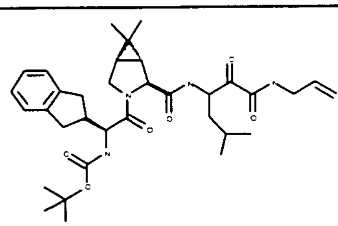
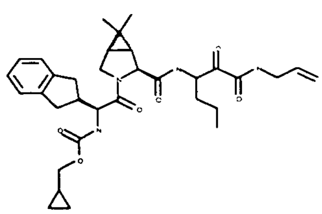
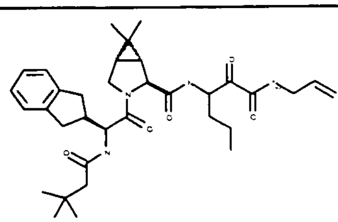
	563	C
	571	C
	572	B
	551	C
	609	C
	593	B
	593	C

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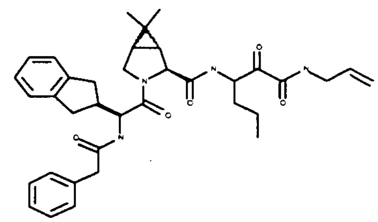
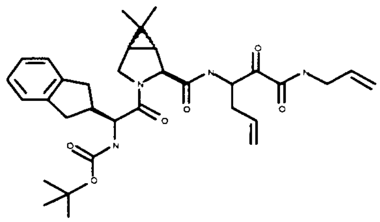
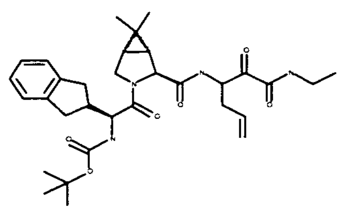
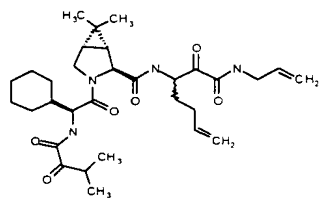
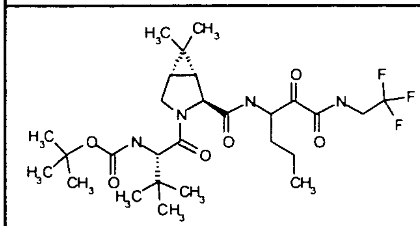
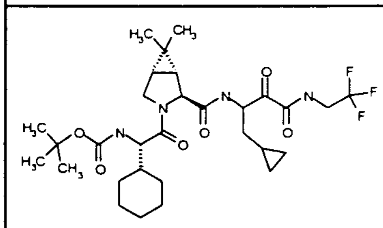
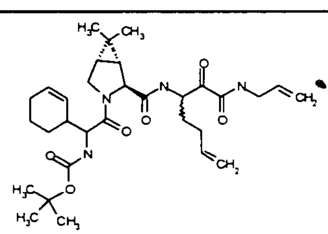
	613	C
	593	B
	581	C
	571	B
	577	C
	615	C
	571	C

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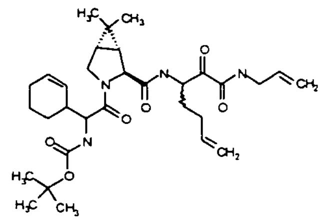
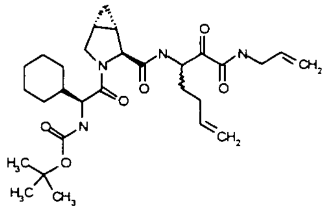
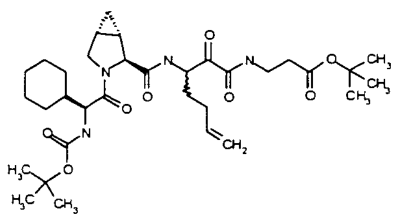
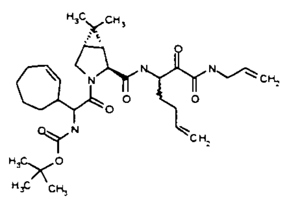
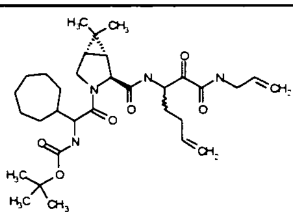
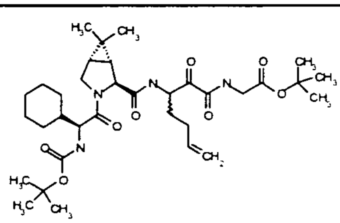
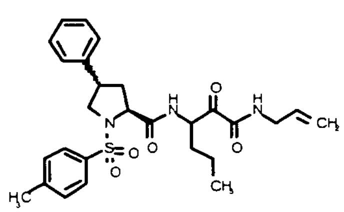
	571	C
	545	C
	633	C
	585	B
	587	B
	647	B
	512	C

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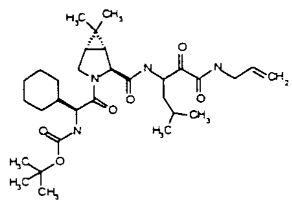
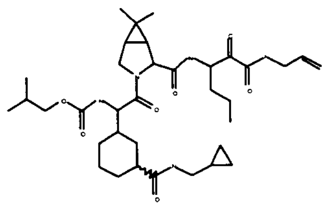
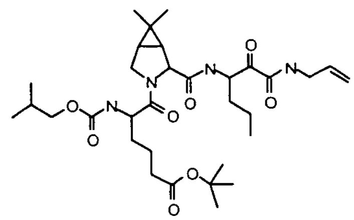
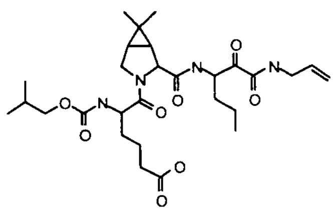
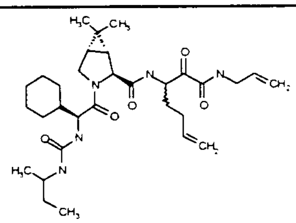
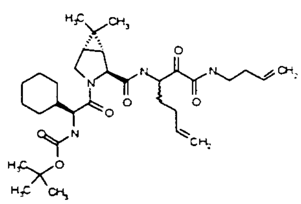
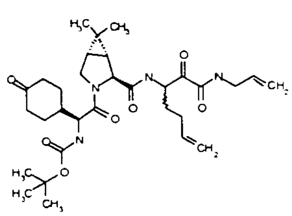
	575	C
	658	C
	621	C
	565	C
	572	A
	587	A
	587	B

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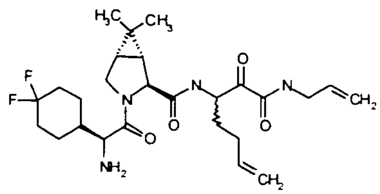
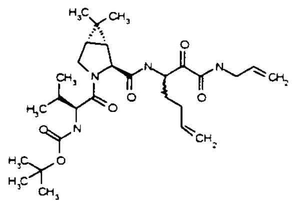
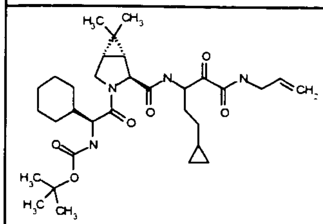
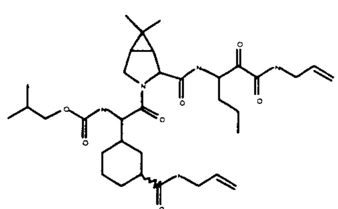
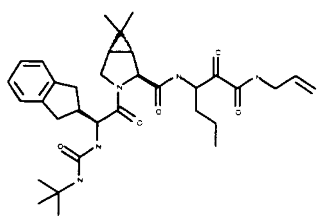
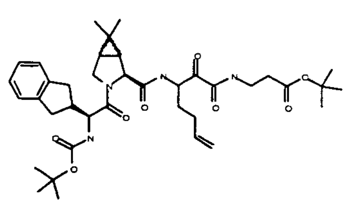
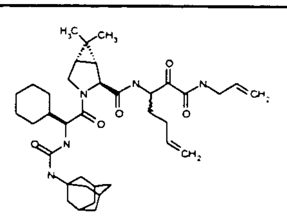
	509	C
	533	C
	587	B
	644	C
	594	B
	695	B
	650	B

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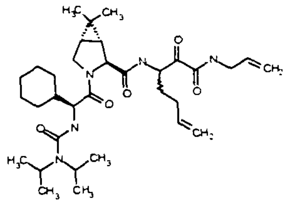
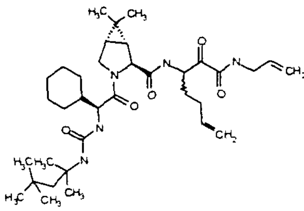
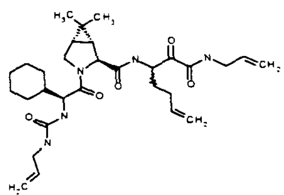
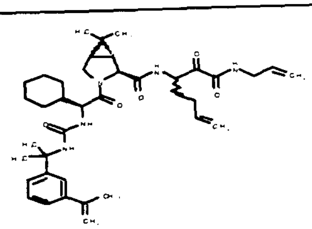
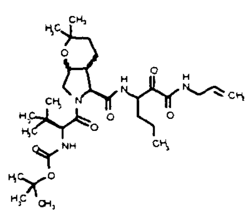
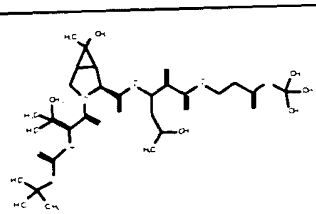
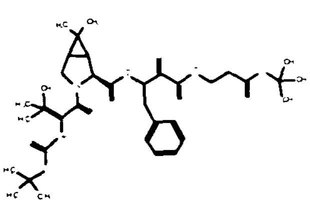
	600	B
	628	A
	556	B
	674	B
	579	C
	637	C
	671	C

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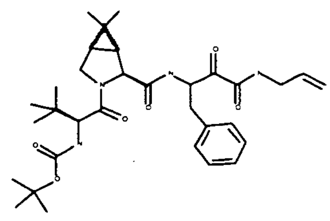
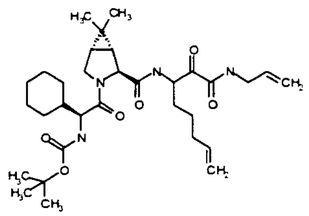
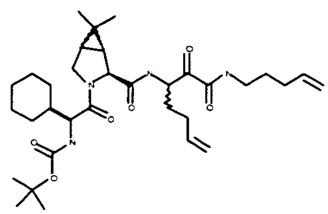
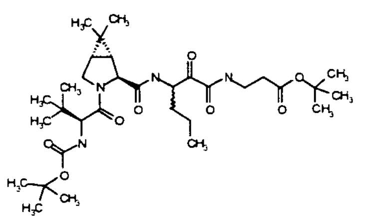
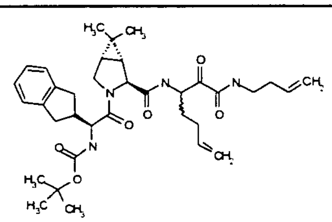
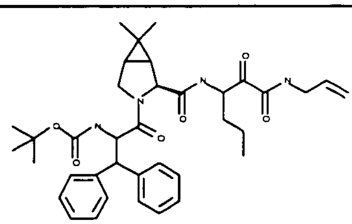
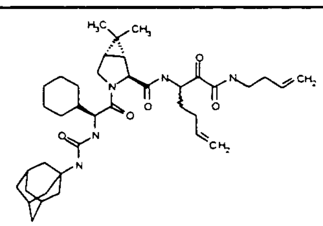
	583	C
	587	B
	601	B
	623	B
	621	A
	645	C
	664	B

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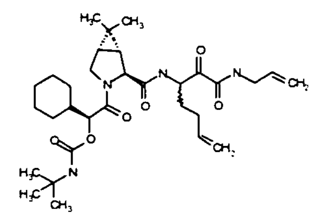
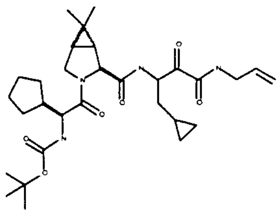
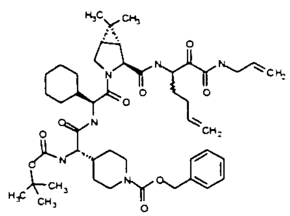
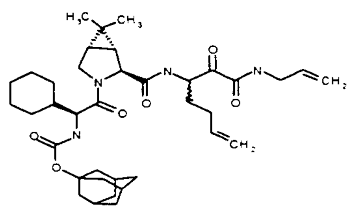
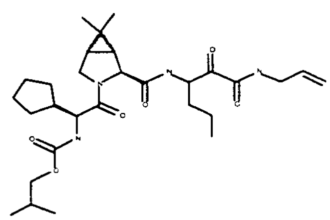
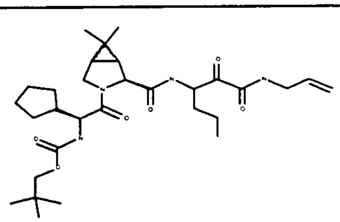
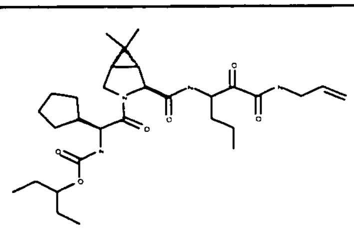
	573	C
	559	C
	847	B
	651	B
	547	C
	561	B
	561	B

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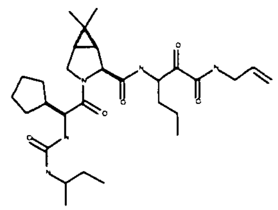
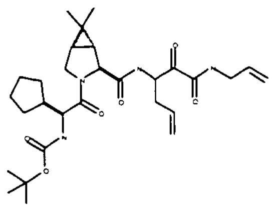
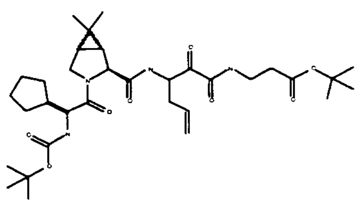
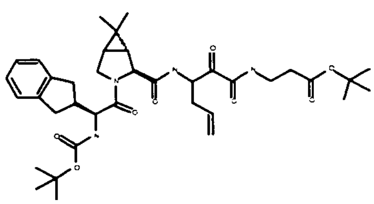
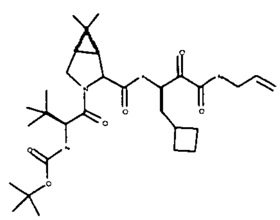
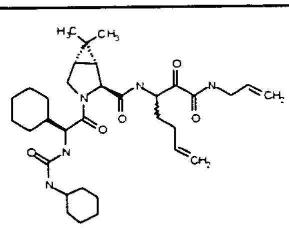
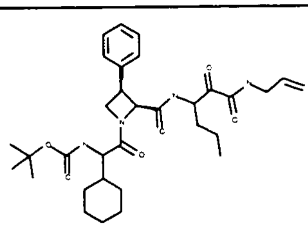
	546	C
	545	C
	633	B
	681	C
	561	C
	598	B
	583	C

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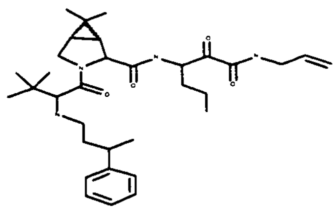
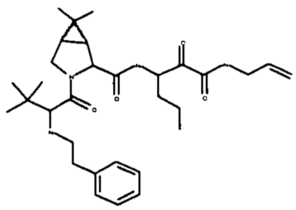
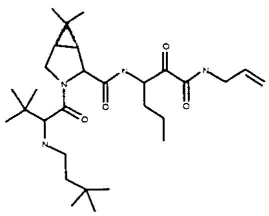
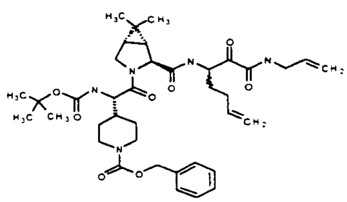
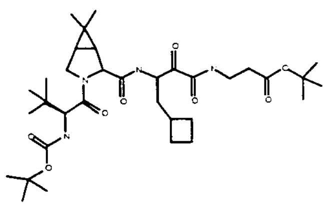
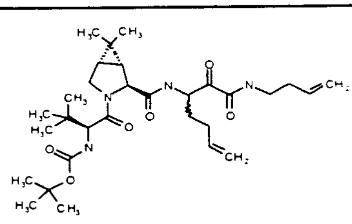
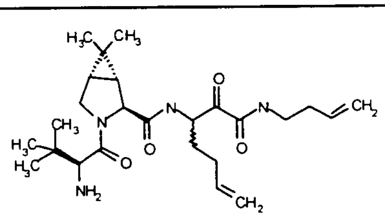
	567	C
	539	C
	519	C
	708	B
	649	C
	561	B
	461	C

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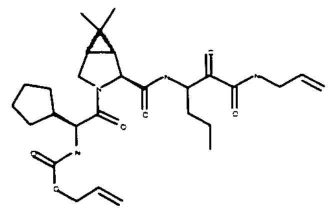
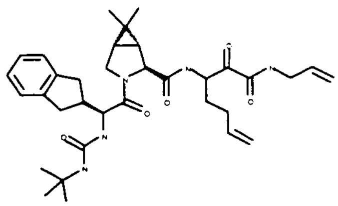
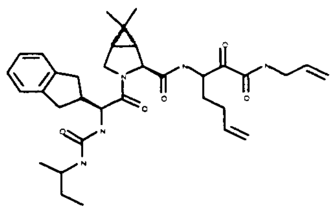
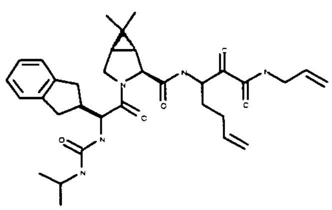
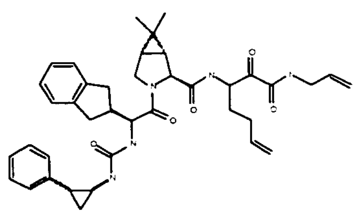
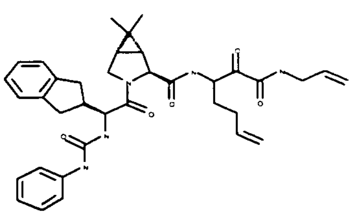
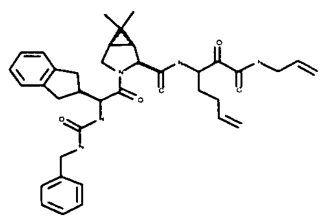
	531	C
	606	A
	606	A
	592	A
	666	C
	626	B
	640	B

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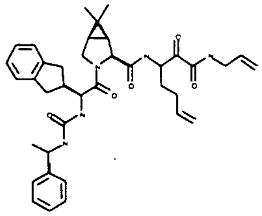
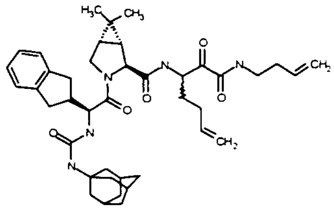
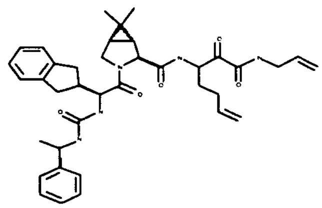
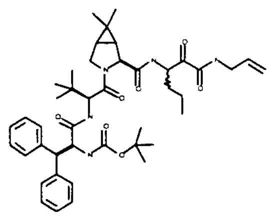
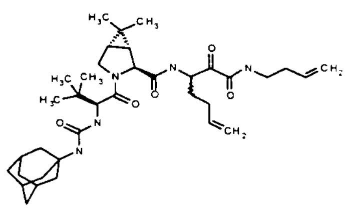
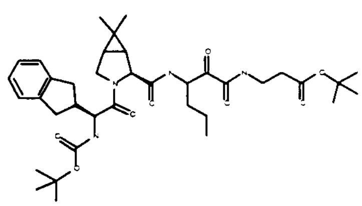
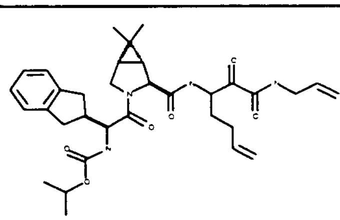
	654	B
	698	B
	654	B
	758	C
	638	A
	683	B
	593	A

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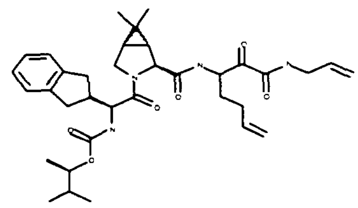
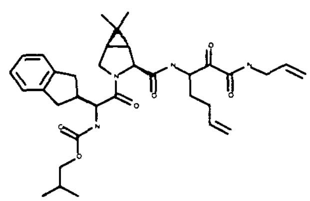
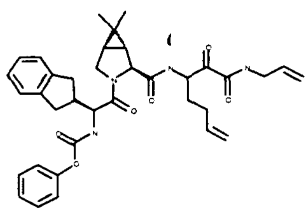
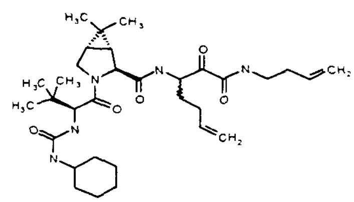
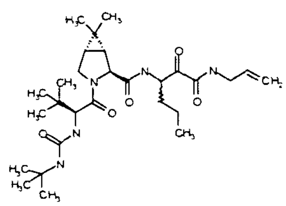
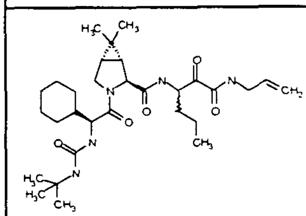
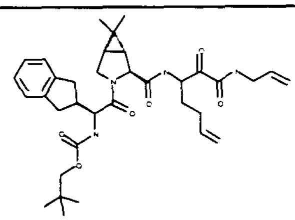
	621	A
	607	B
	627	B
	586	A
	534	B
	560	C
	621	A

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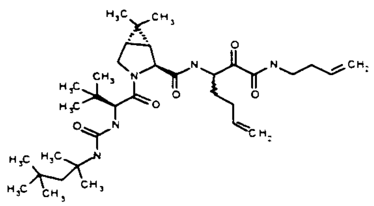
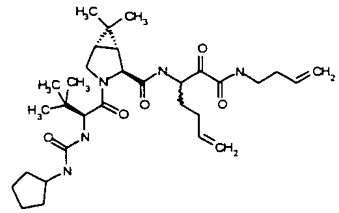
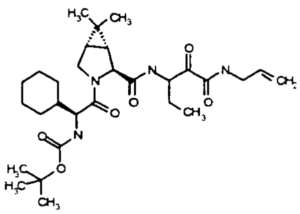
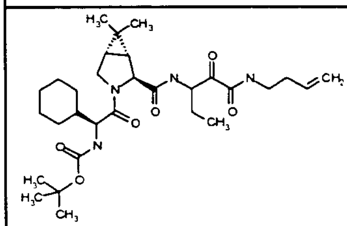
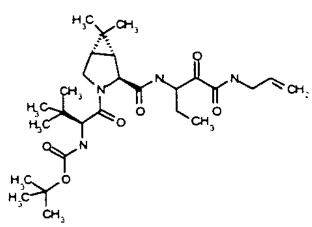
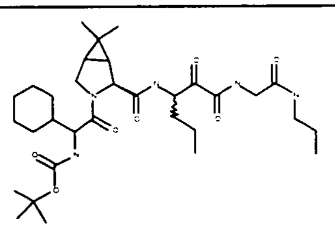
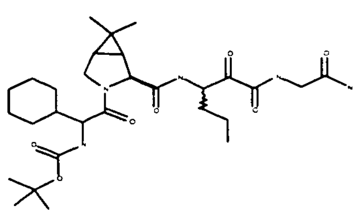
	616	B
	572	A
	547	C
	561	C
	521	C
	620	B
	578	B

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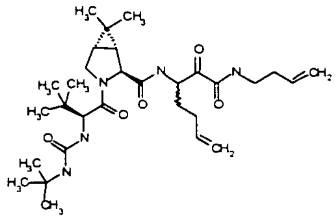
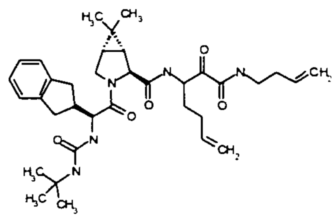
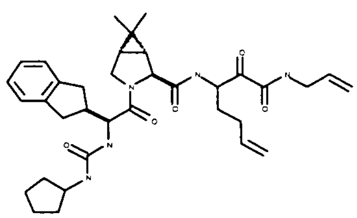
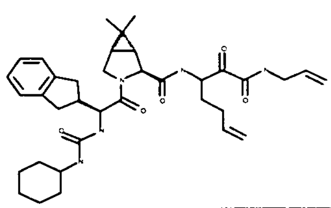
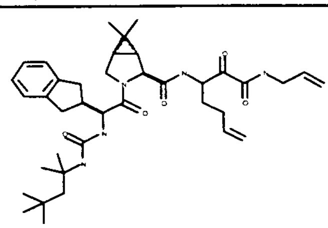
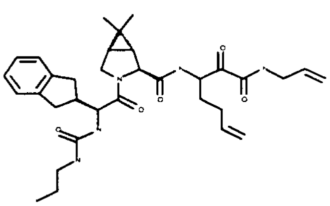
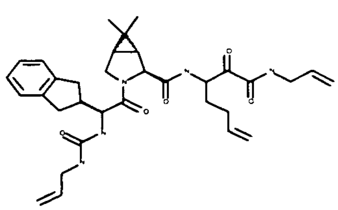
	560	A
	620	A
	618	B
	632	B
	662	B
	592	B
	590	B

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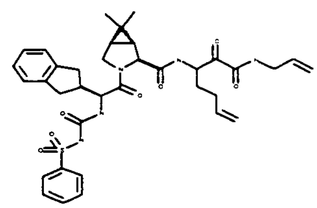
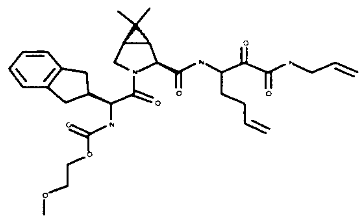
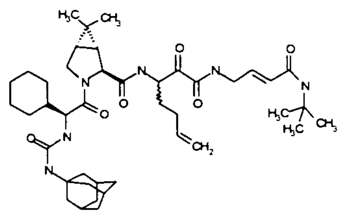
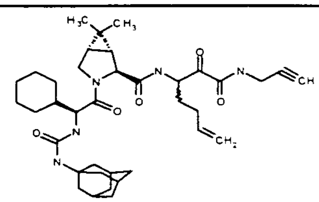
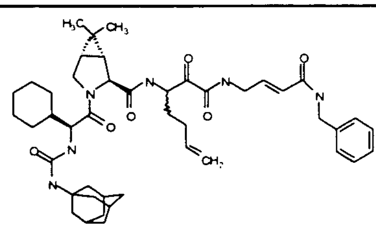
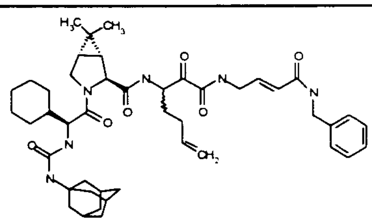
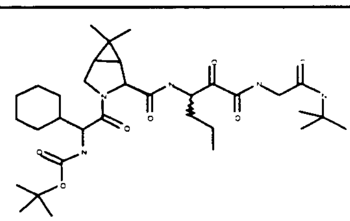
	690	B
	609	B
	749	B
	648	A
	783	B
	783	B
	634	C

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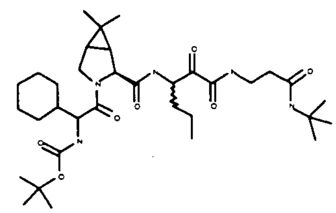
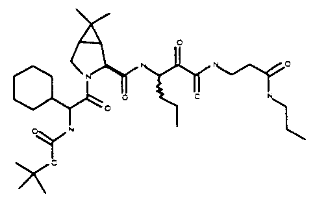
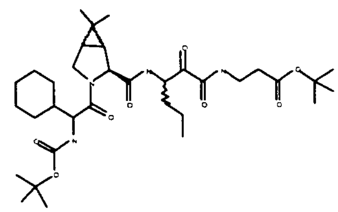
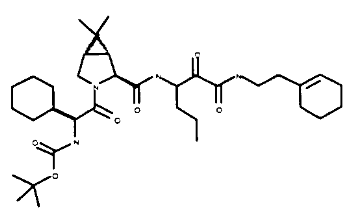
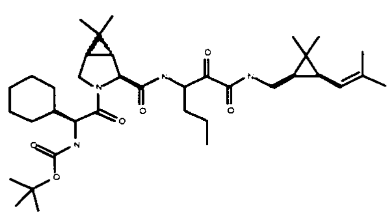
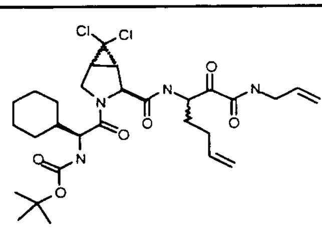
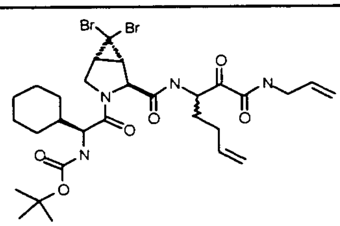
	648	C
	634	C
	649	C
	629	C
	657	C
	614	A
	702	B

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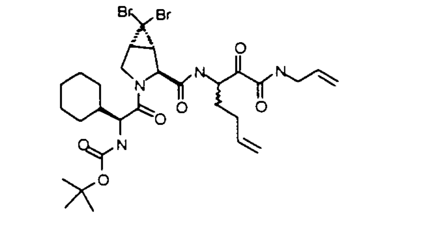
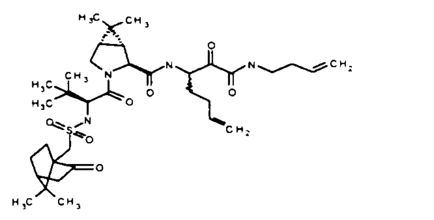
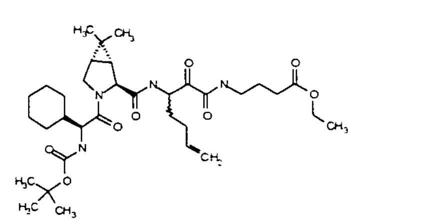
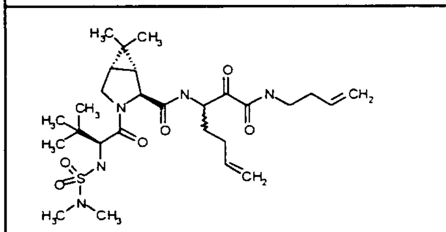
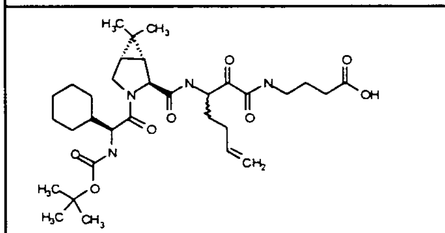
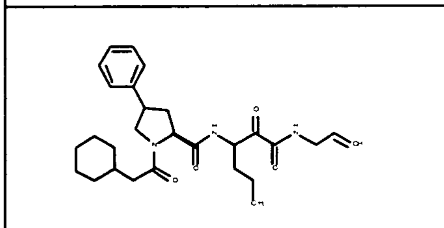
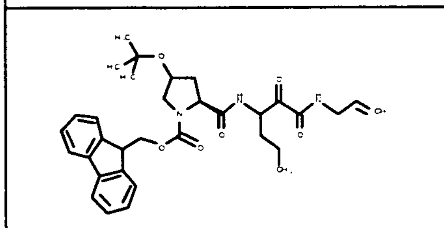
	702	A
	675	B
	647	B
	568	C
	619	C
	482	C
	576	C

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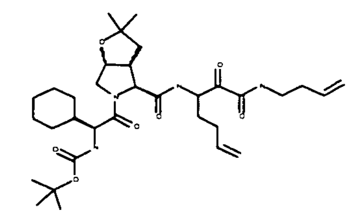
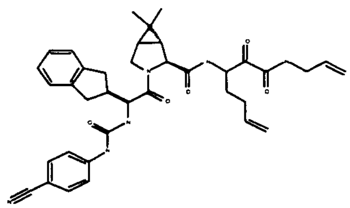
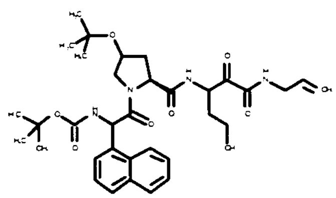
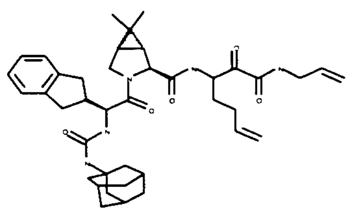
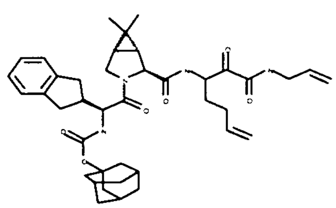
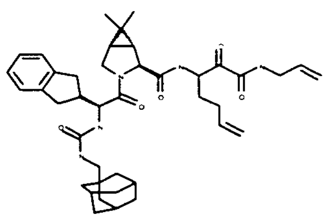
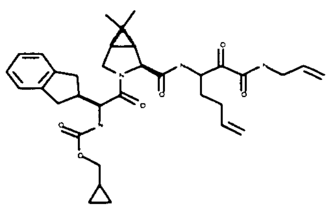
	617	B
	651	C
	637	C
	684	B
	685	B
	698	B
	605	B

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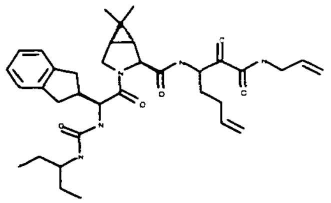
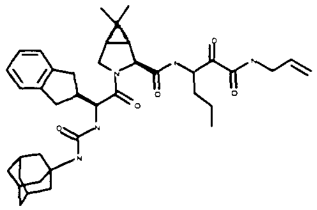
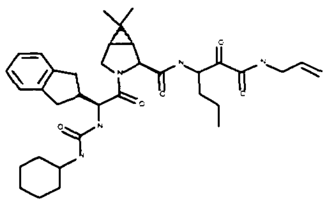
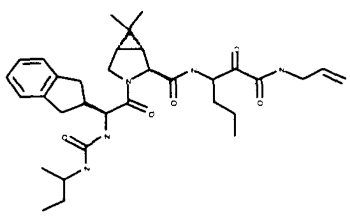
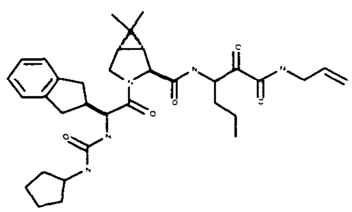
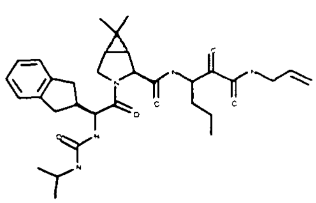
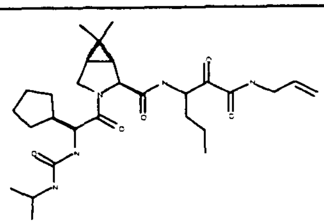
	620	B
	672	C
	620	B
	594	B
	606	B
	580	C
	532	B

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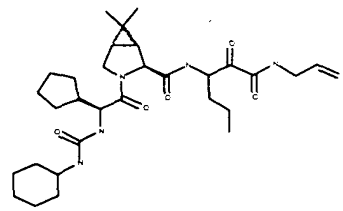
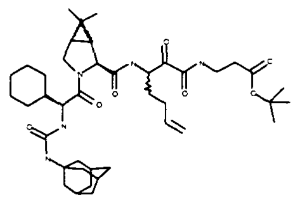
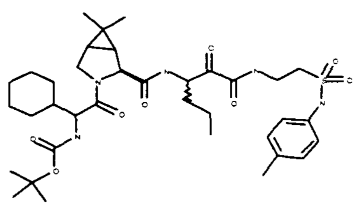
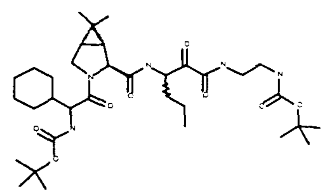
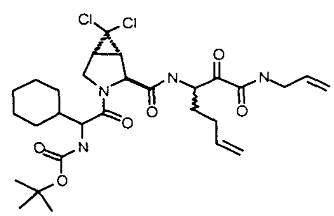
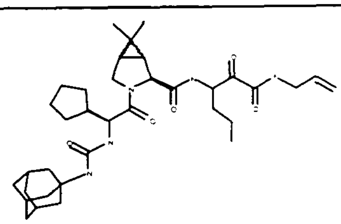
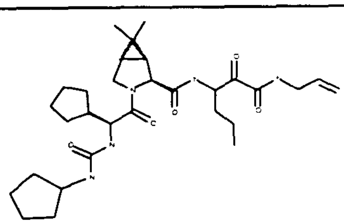
	572	B
	738	A
	718	B
	664	B
	614	B
	624	B
	558	B

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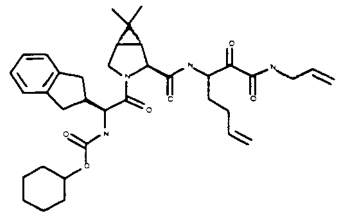
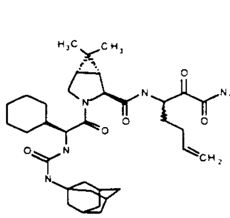
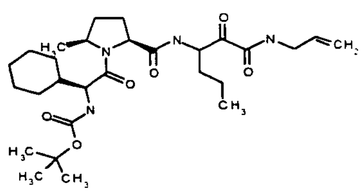
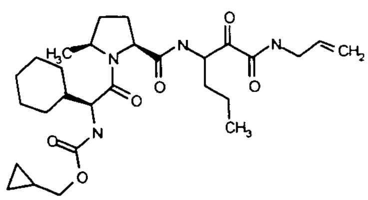
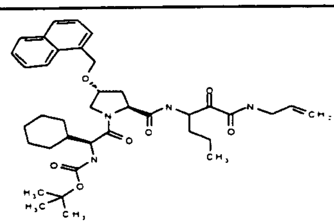
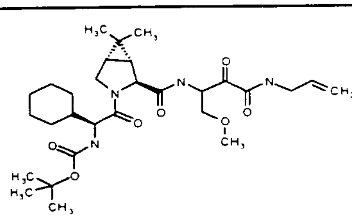
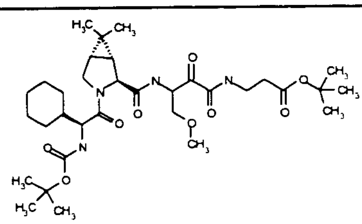
	633	B
	770	C
	535	C
	533	C
	677	C
	563	B
	651	A

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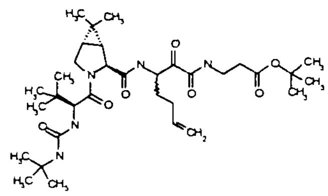
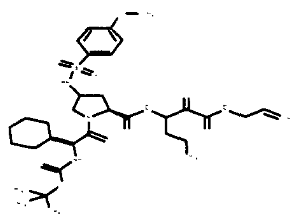
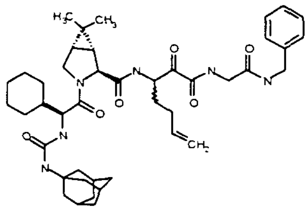
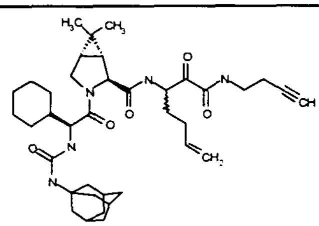
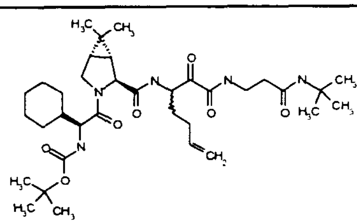
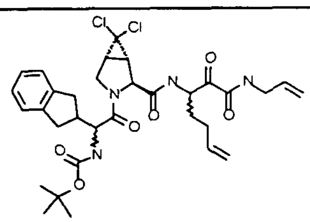
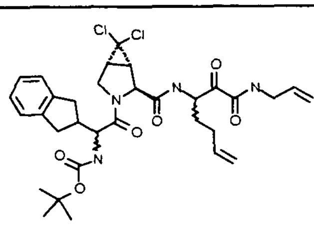
	634	A
	706	C
	757	A
	662	A
	660	A
	648	A
	648	C

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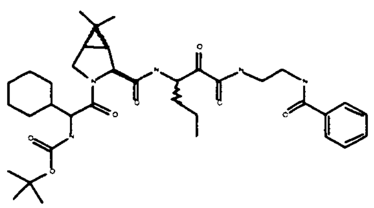
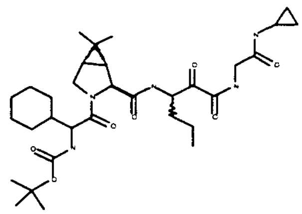
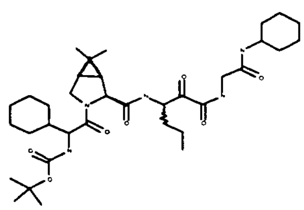
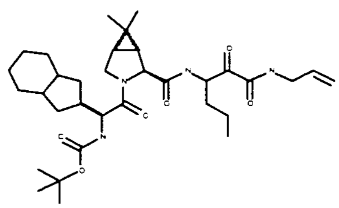
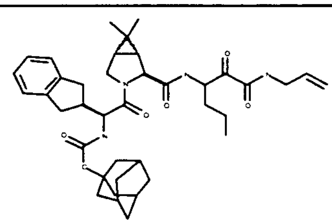
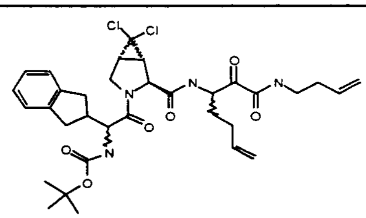
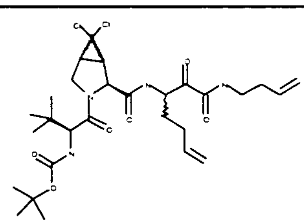
	668	B
	618	A
	660	B
	601	B
	673	B
	662	A
	602	A

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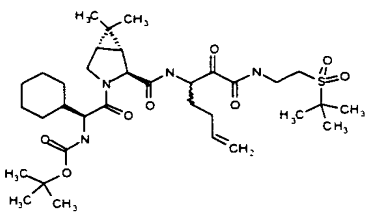
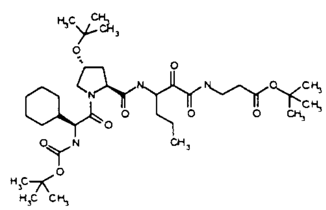
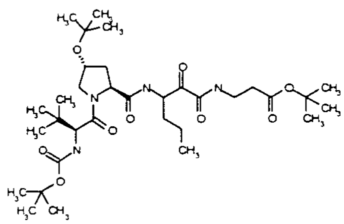
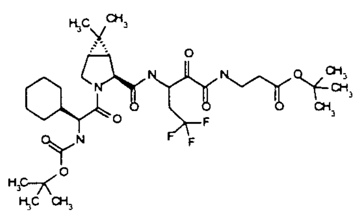
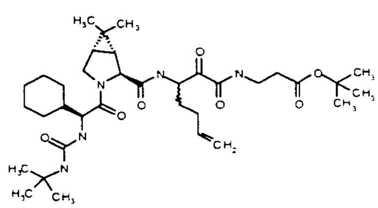
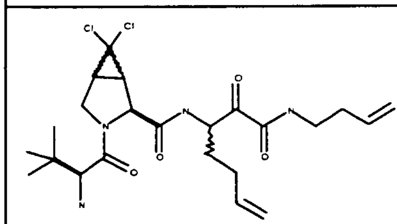
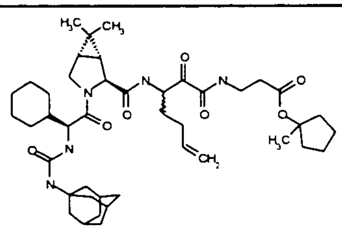
	681	A
	681	C
	655	C
	689	B
	660	A
	538	C
	764	A

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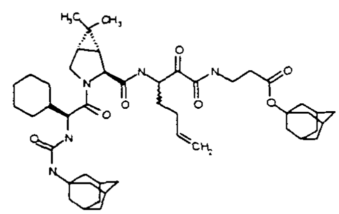
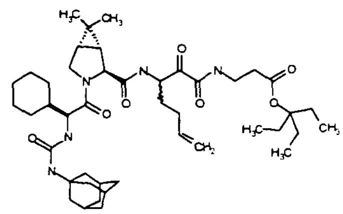
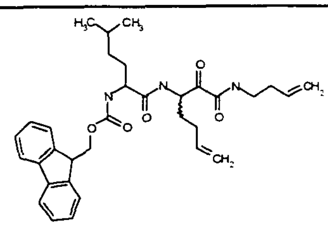
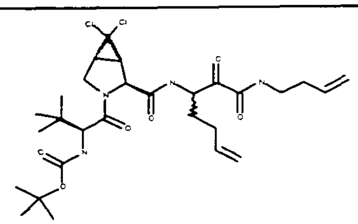
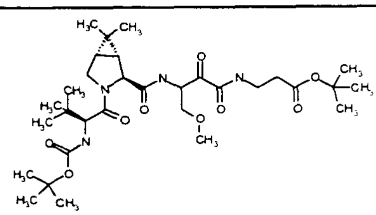
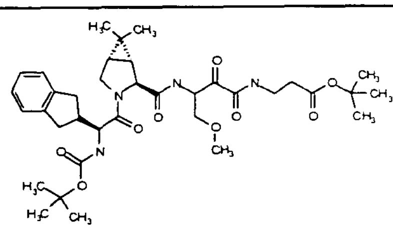
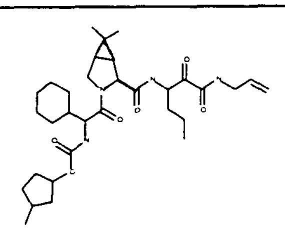
	816	C
	780	B
	560	C
	602	C
	625	B
	685	B
	587	A

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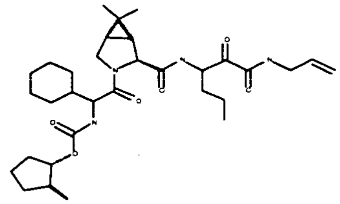
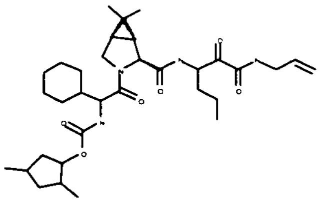
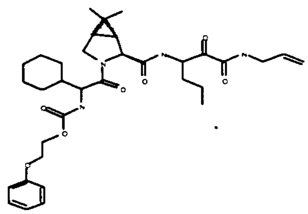
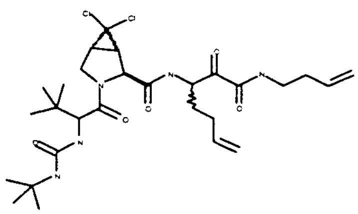
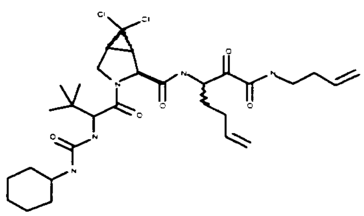
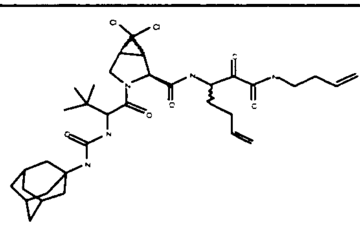
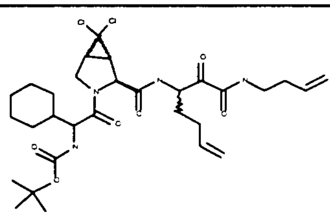
	587	A
	601	A
	625	B
	601	A
	627	B
	679	A
	628	A

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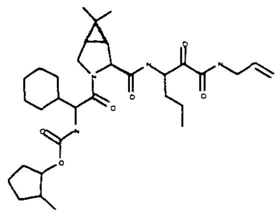
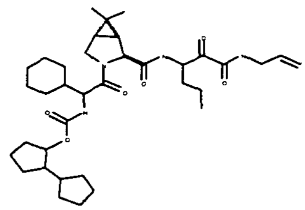
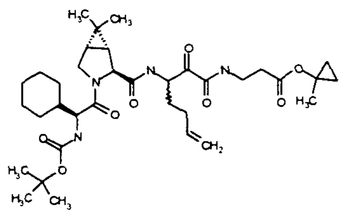
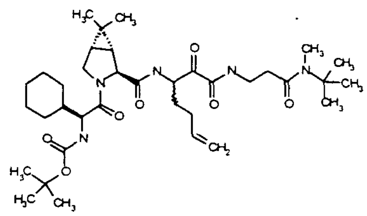
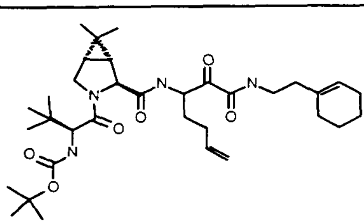
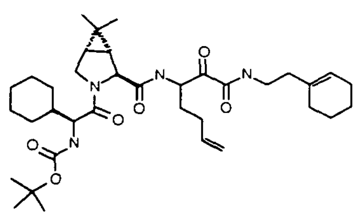
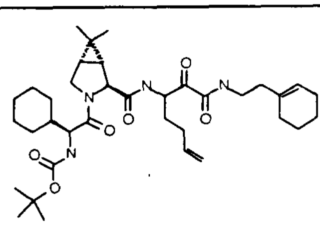
	587	A
	641	A
	659	A
	674	A
	615	B
	641	B
	641	B

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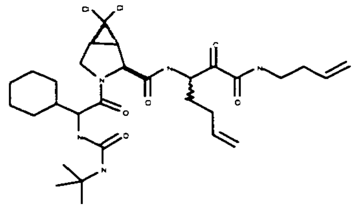
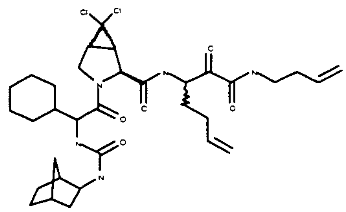
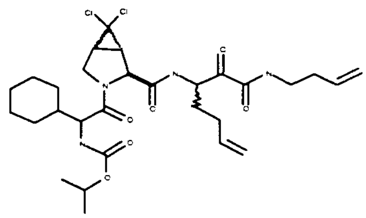
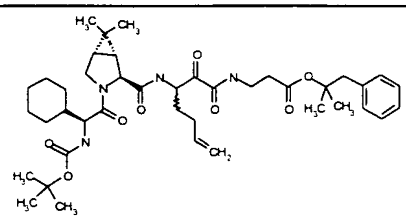
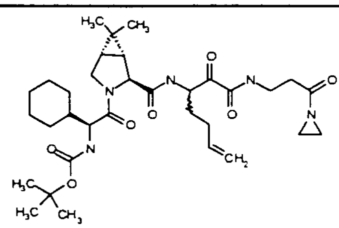
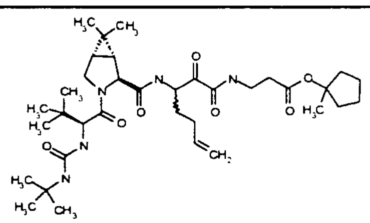
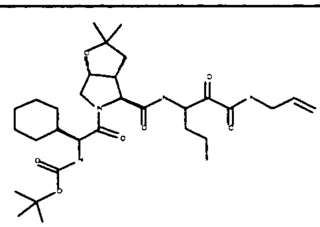
	627	A
	665	A
	614	A
	737	B
	666	A
	660	A
	591	C

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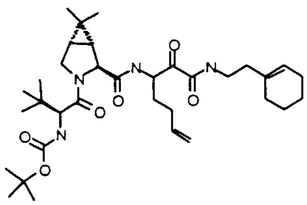
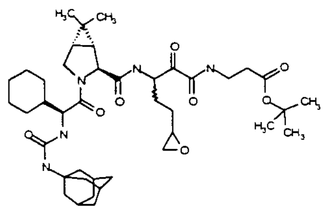
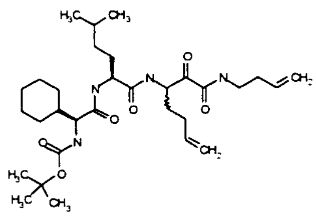
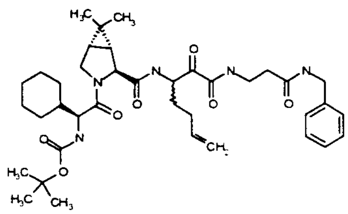
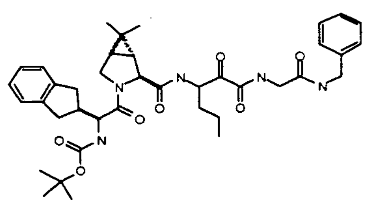
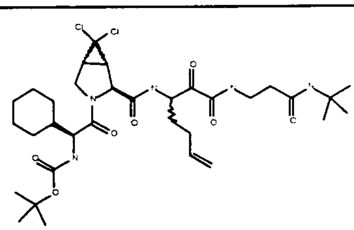
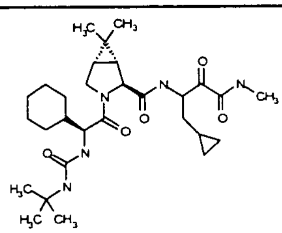
	615	C
	754	B
	577	C
	694	A
	702	A
	701	A
	546	B

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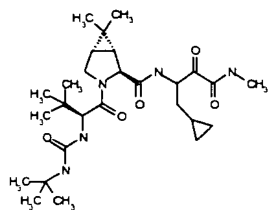
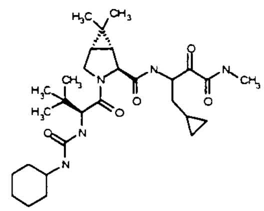
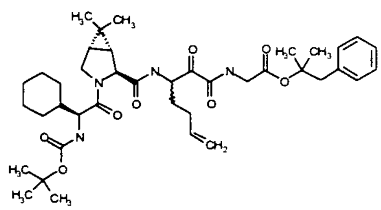
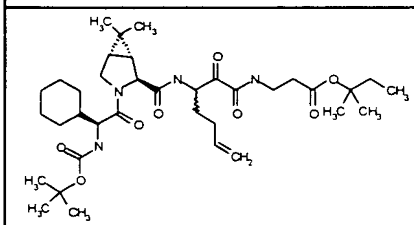
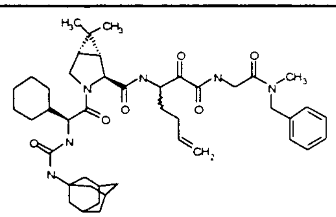
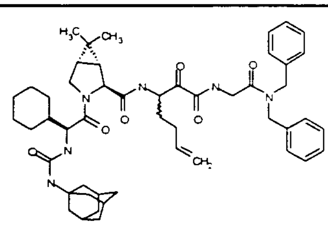
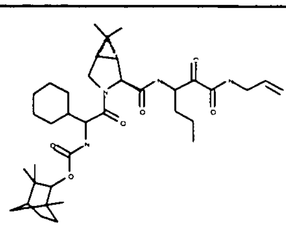
	520	B
	546	B
	723	B
	675	A
	771	B
	847	C
	641	A

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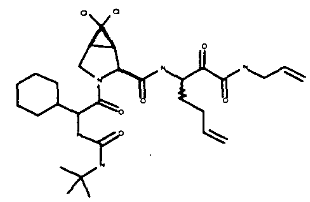
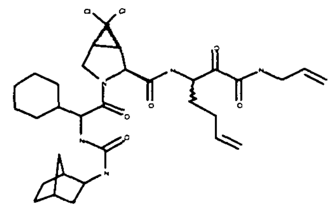
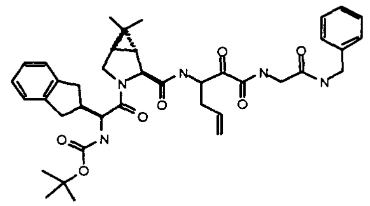
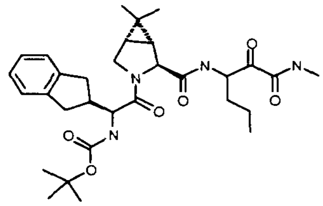
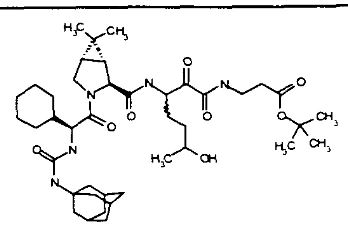
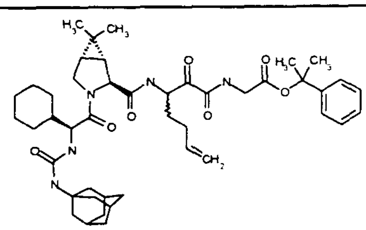
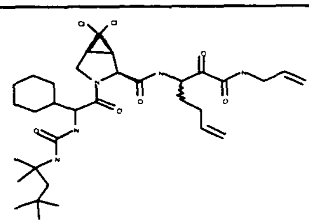
	613	A
	651	C
	700	A
	569	A
	756	B
	786	A
	669	B

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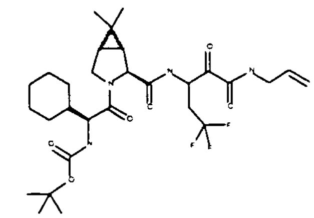
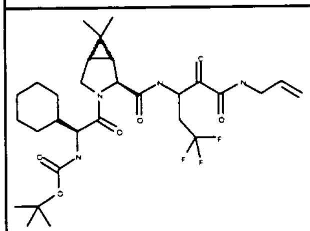
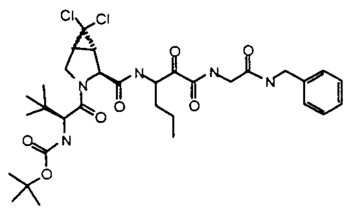
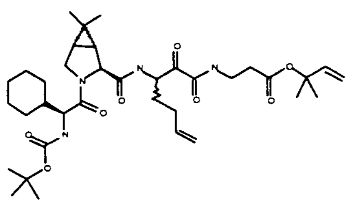
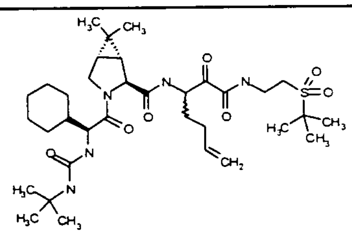
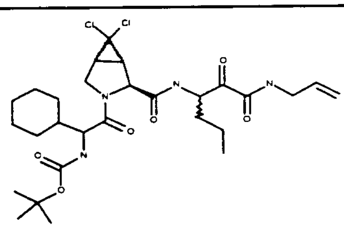
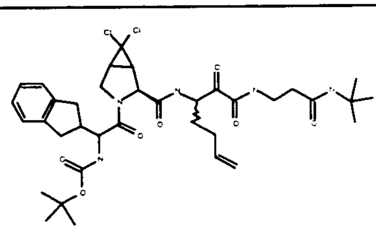
	601	A
	601	B
	683	A
	673	A
	680	A
	602	A
	735	A

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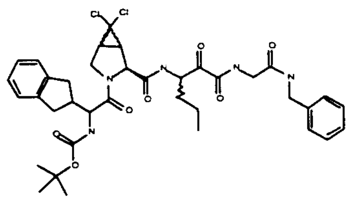
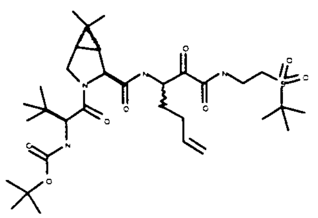
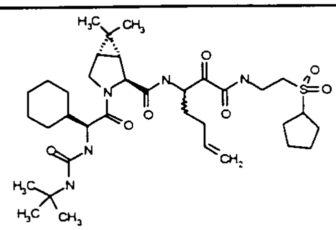
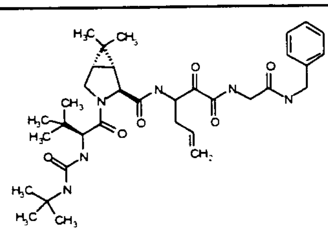
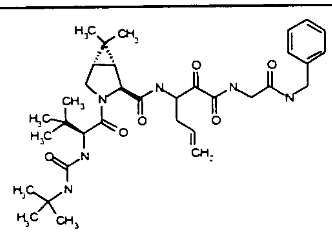
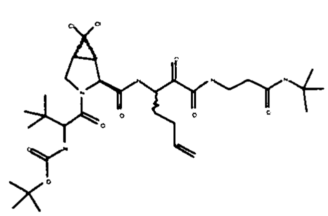
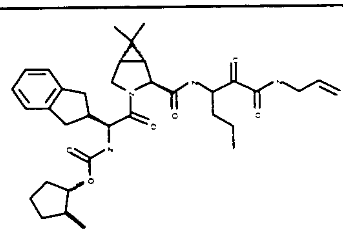
	743	A
	655	B
	692	A
	639	A
	639	A
	675	A
	621	A

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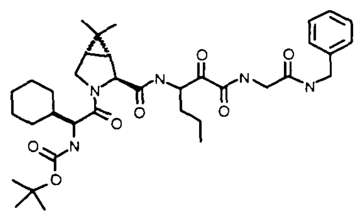
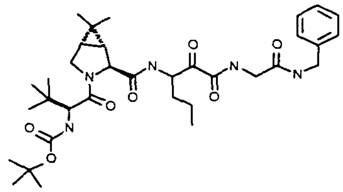
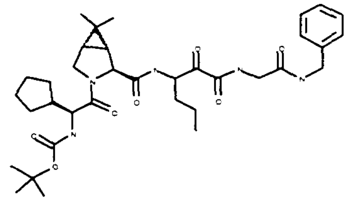
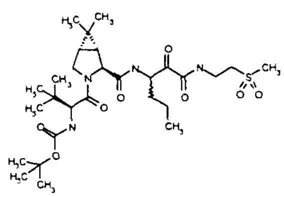
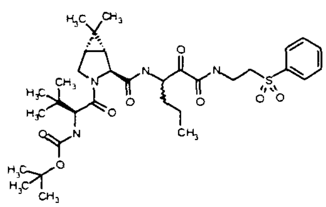
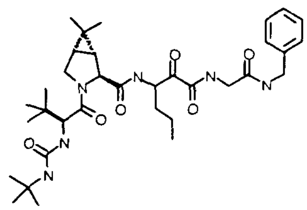
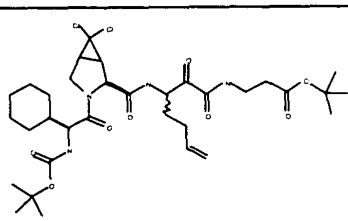
	668	A
	642	A
	654	A
	601	C
	663	B
	641	A
	702	A

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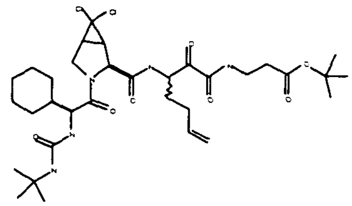
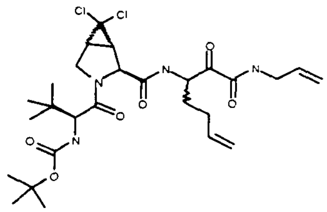
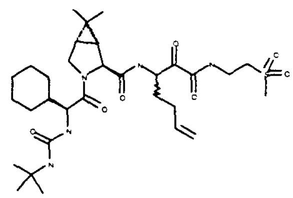
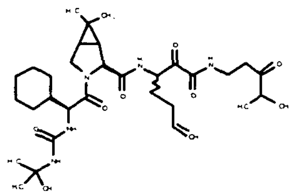
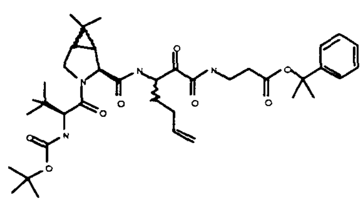
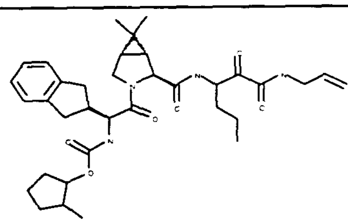
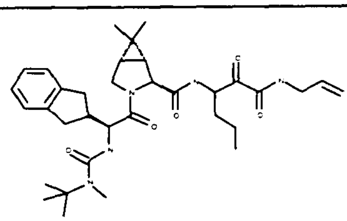
	701	A
	588	B
	638	A
	630	A
	697	A
	621	A
	608	B

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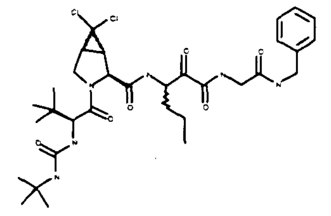
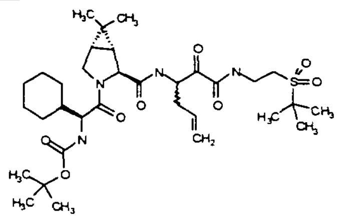
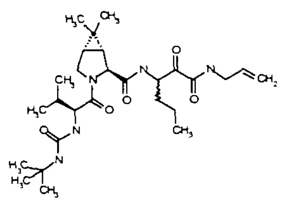
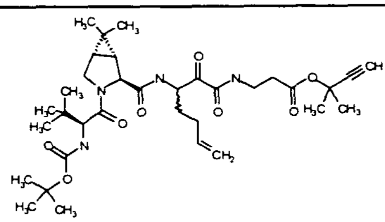
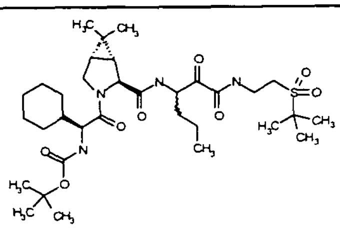
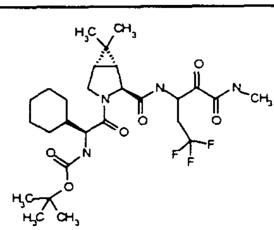
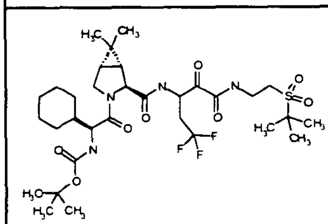
	682	A
	667	B
	520	B
	645	B
	669	C
	575	A
	709	B

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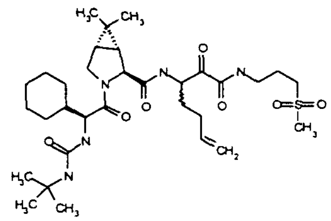
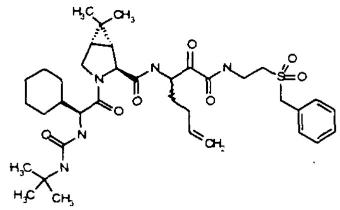
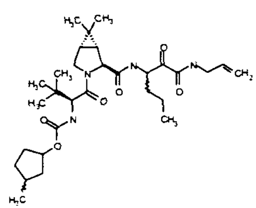
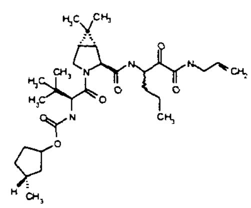
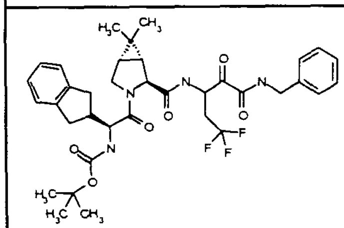
	652	B
	714	A
	561	B
	561	B
	685	B

Table5

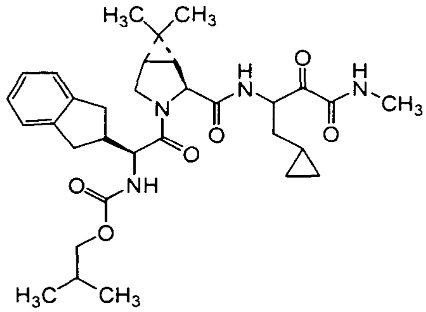
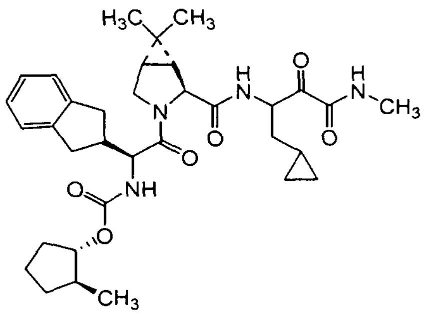
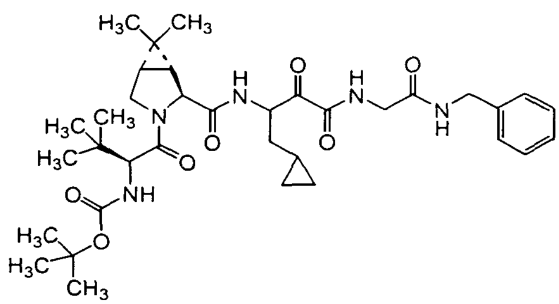
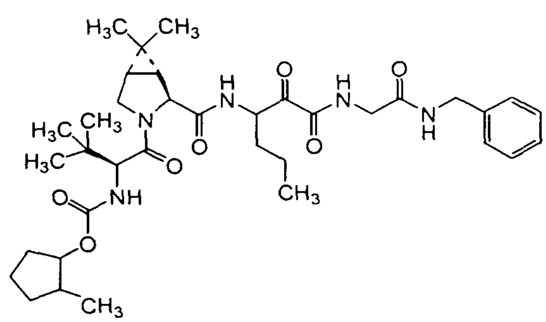
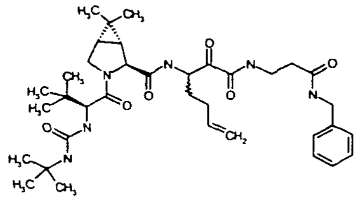
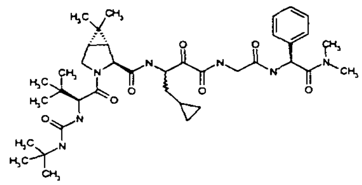
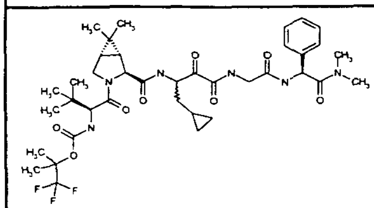
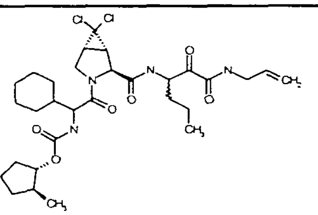
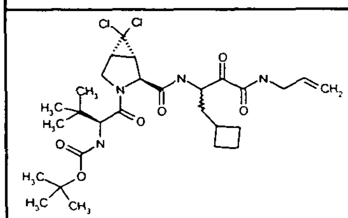
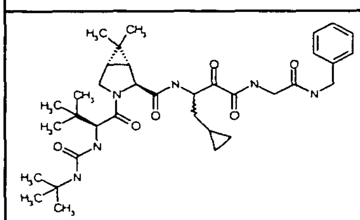
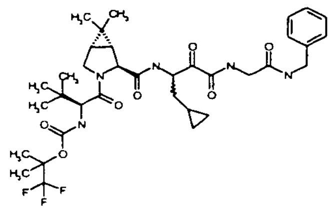
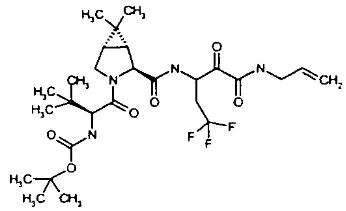
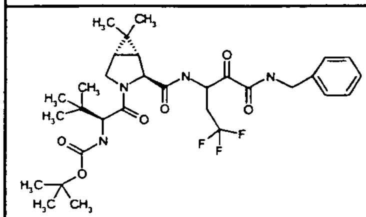
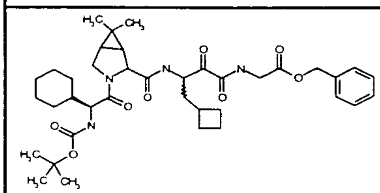
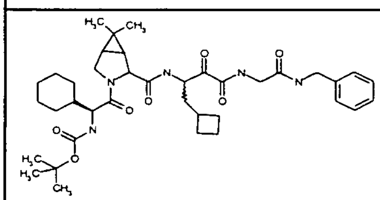
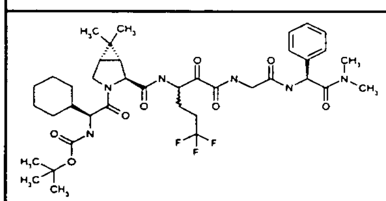
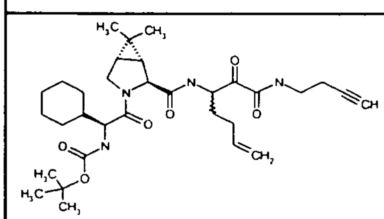
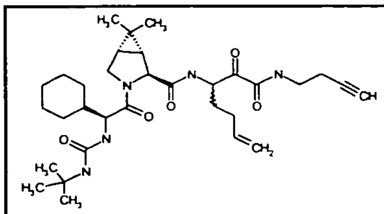
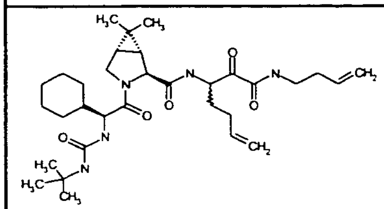
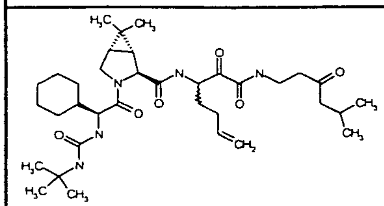
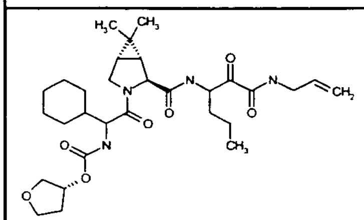
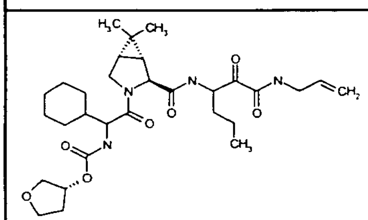
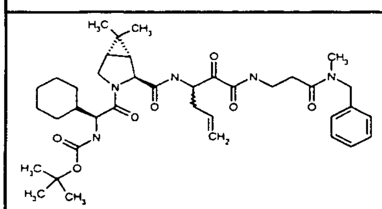
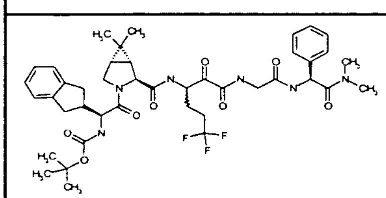
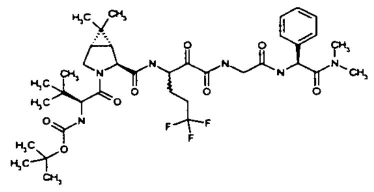
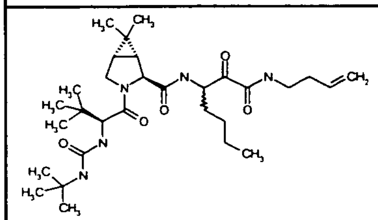
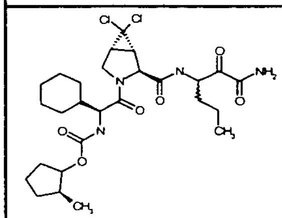
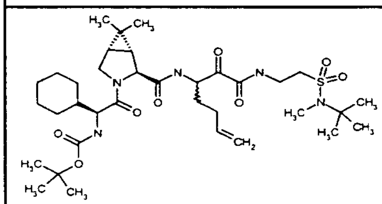
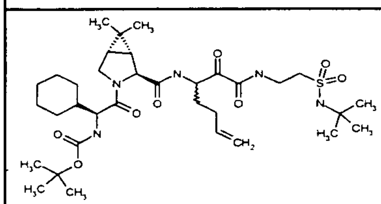
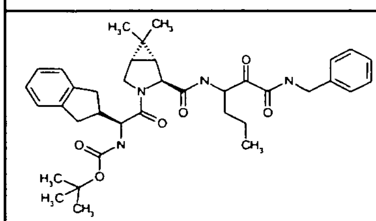
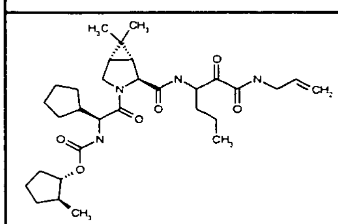
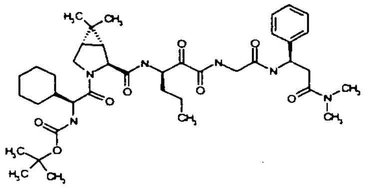
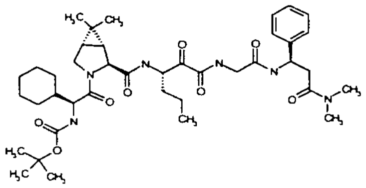
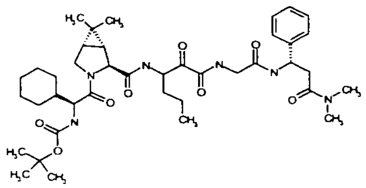
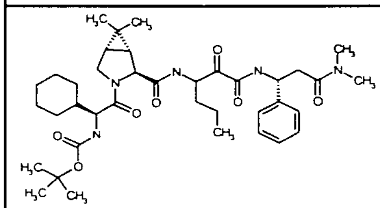
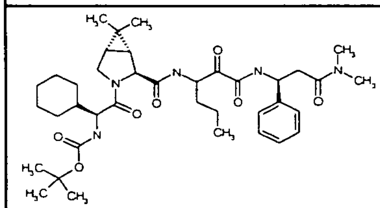
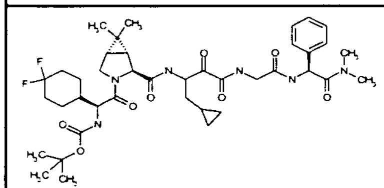
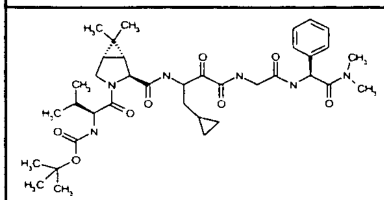
Structure	MW	Ki* Range
	580	A
	606	A
	653	A
	667	A

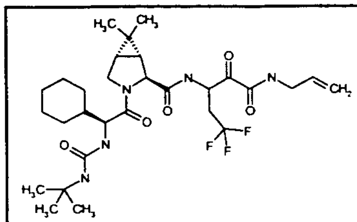
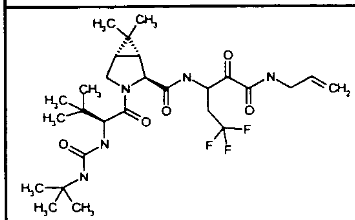
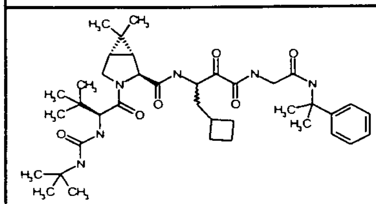
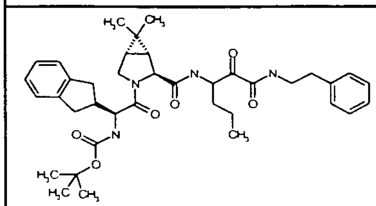
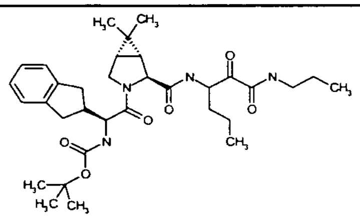
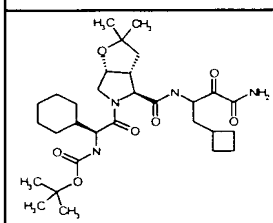
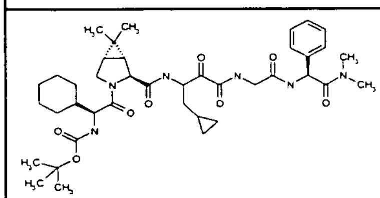
TABLE 6 STRUCTURE	MW	Ki* (nM)
	666.87	A
	723.92	A
	778.88	A
	627.61	A
	601.58	B
	652.84	A

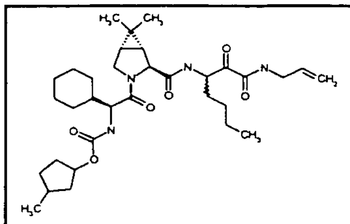
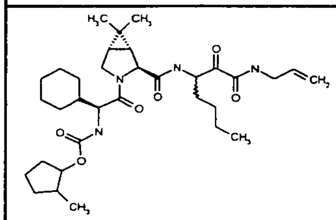
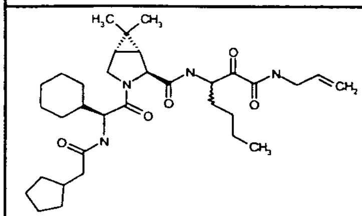
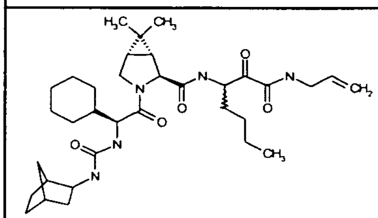
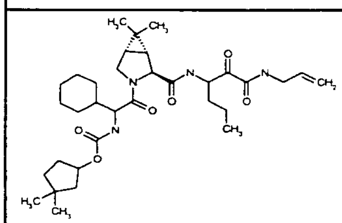
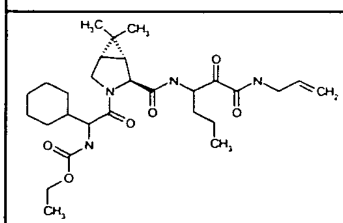
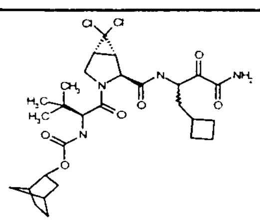
	707.80	A
	574.65	B
	624.71	B
	694.88	A
	693.89	B
	792.90	A
	584.76	A

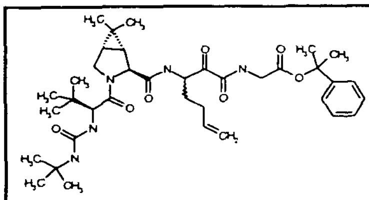
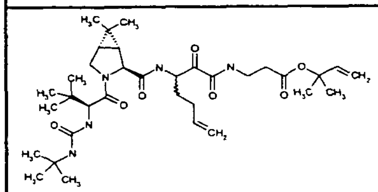
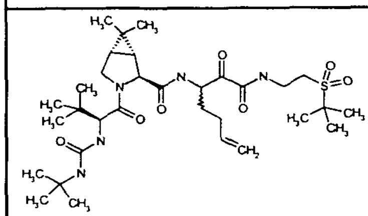
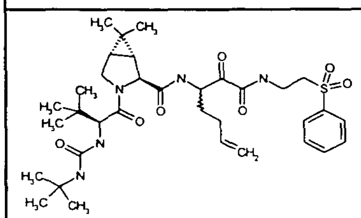
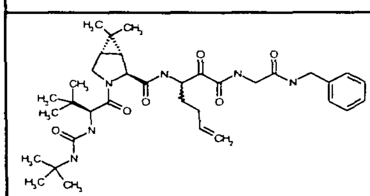
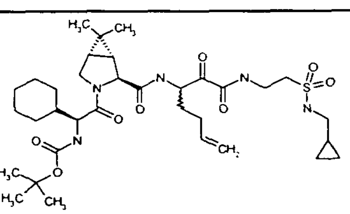
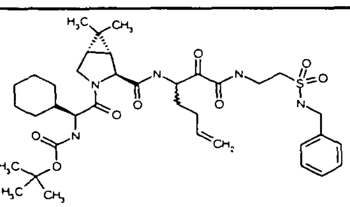
	583.78	A
	585.79	A
	643.87	A
	574.72	B
	574.72	B
	693.89	B
	826.92	A

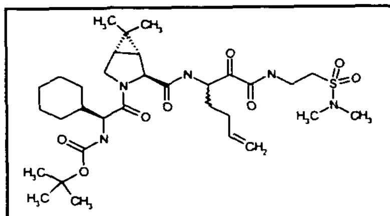
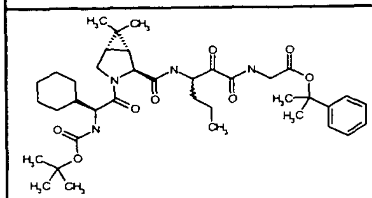
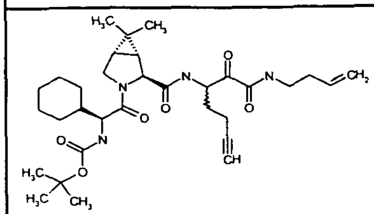
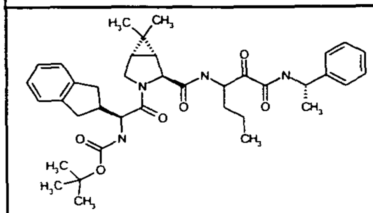
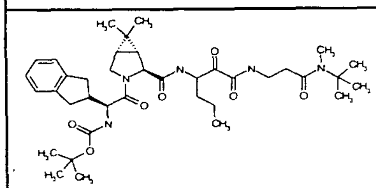
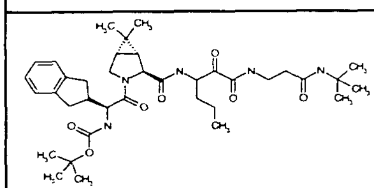
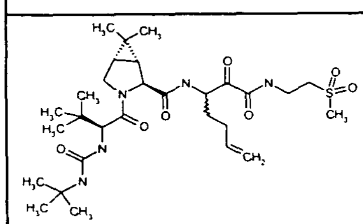
	766.87	A
	561.77	B
	587.55	A
	709.95	A
	695.93	B
	644.82	B
	572.75	A

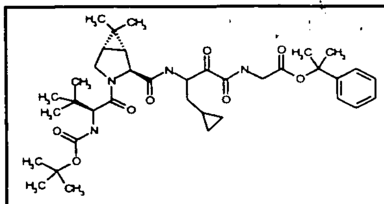
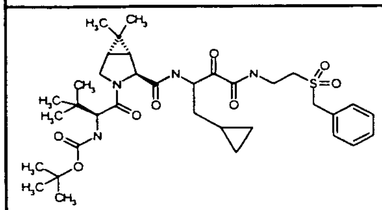
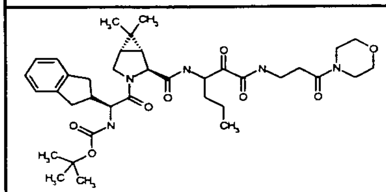
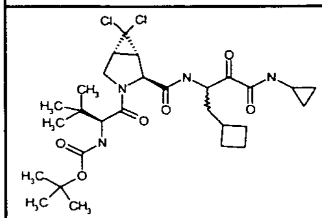
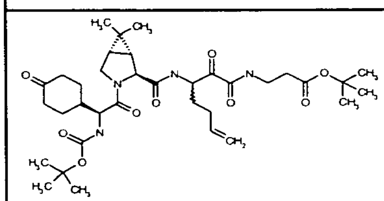
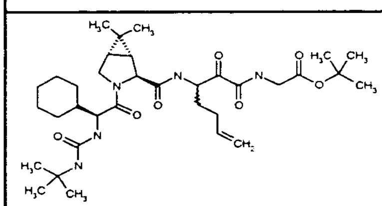
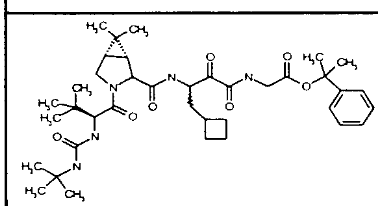
	752.96	A
	752.96	A
	752.96	A
	695.91	C
	695.91	B
	786.92	A
	710.88	A

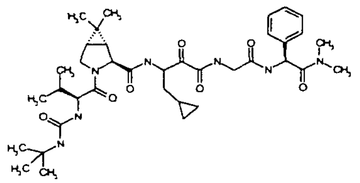
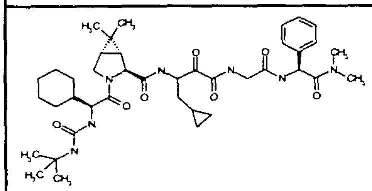
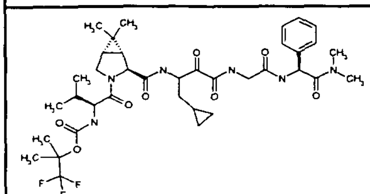
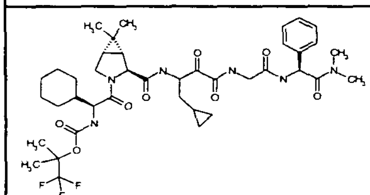
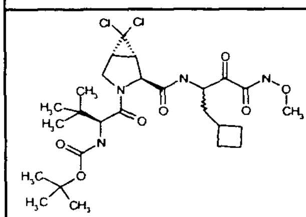
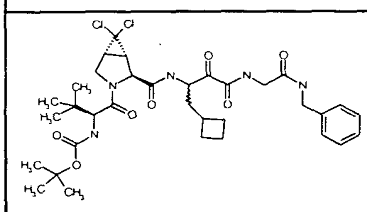
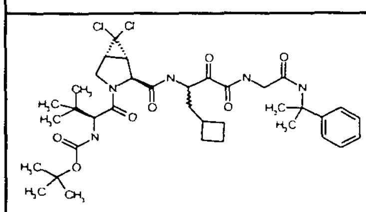
	599.70	A
	573.66	B
	694.92	B
	658.85	B
	596.77	B
	576.74	B
	750.94	A

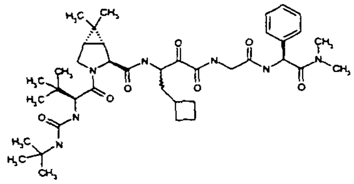
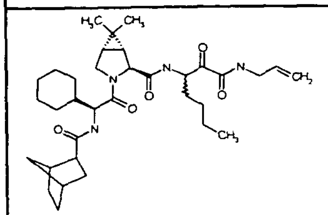
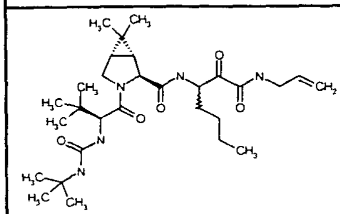
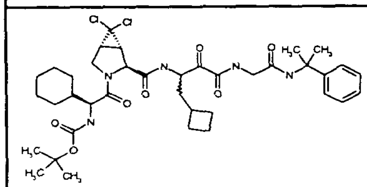
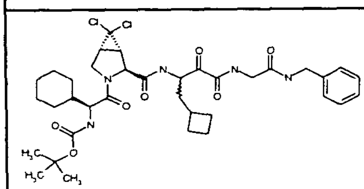
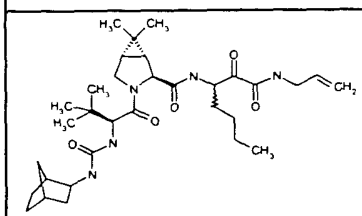
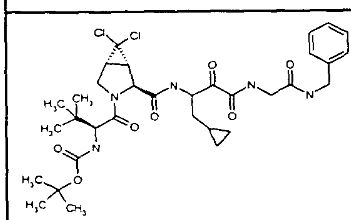
	600.81	B
	600.81	B
	584.81	B
	611.83	A
	600.81	B
	532.69	B
	599.56	A

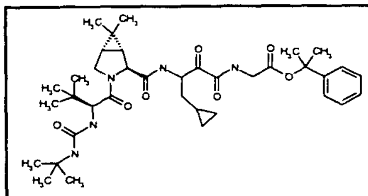
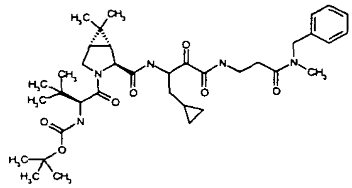
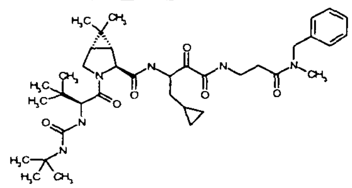
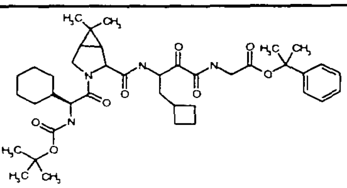
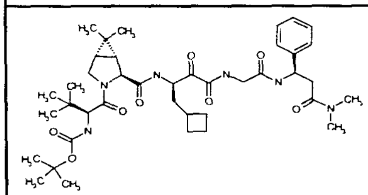
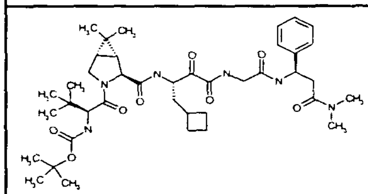
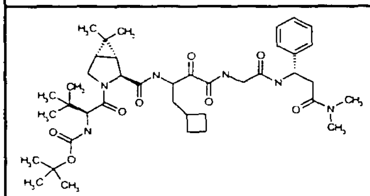
	681.88	A
	645.85	A
	653.89	B
	673.88	A
	652.84	A
	693.91	A
	729.94	A

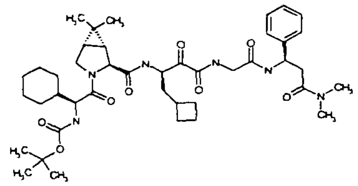
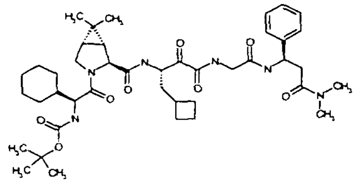
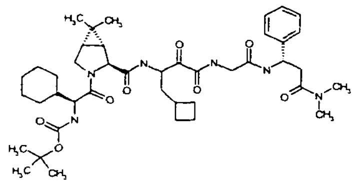
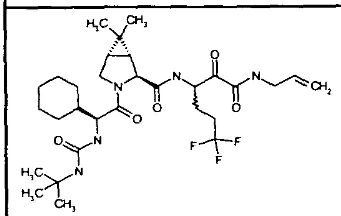
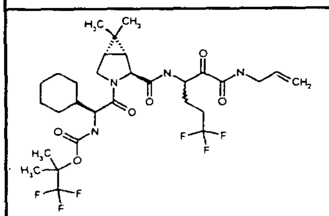
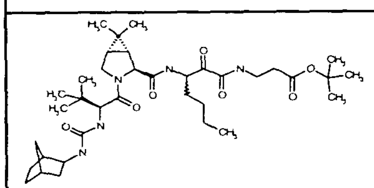
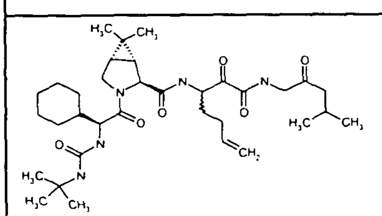
	667.87	A
	696.89	A
	584.76	A
	658.85	A
	695.91	B
	681.88	B
	611.81	B

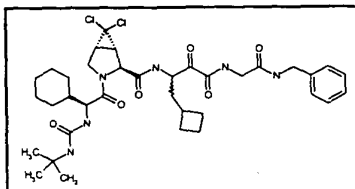
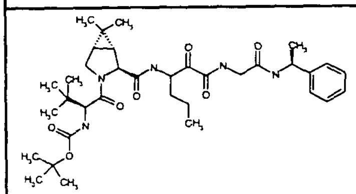
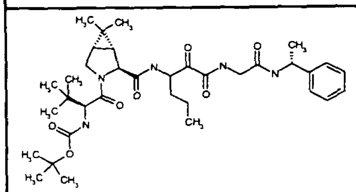
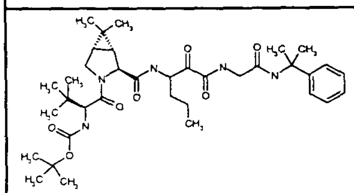
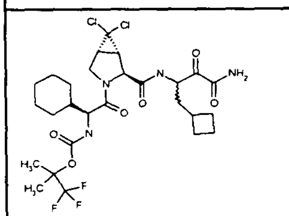
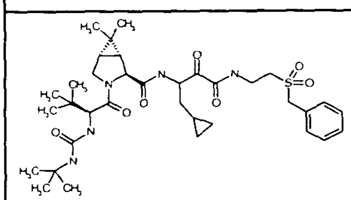
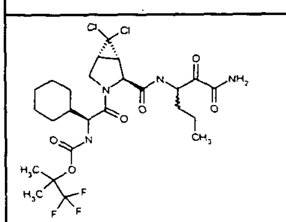
	682.87	A
	688.89	A
	695.86	B
	601.58	B
	674.84	A
	645.85	B
	695.91	A

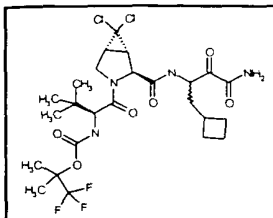
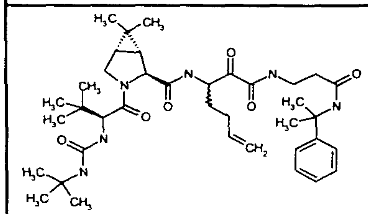
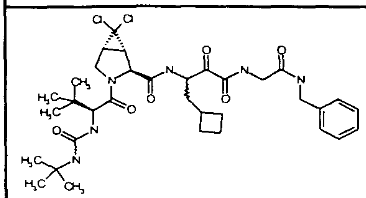
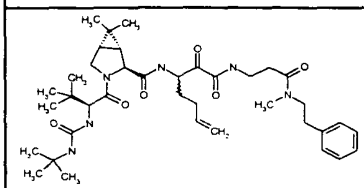
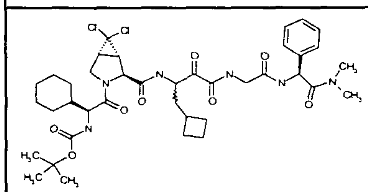
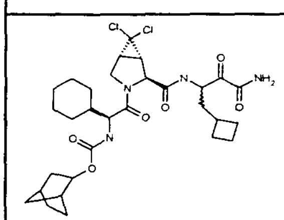
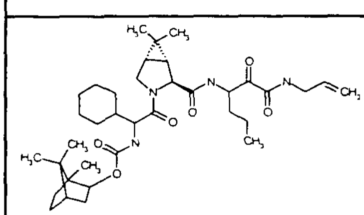
	709.89	A
	749.96	A
	764.85	A
	804.92	A
	591.54	A
	708.69	C
	736.74	C

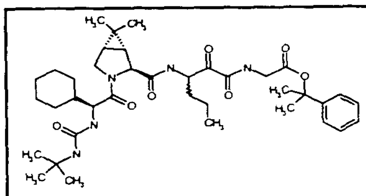
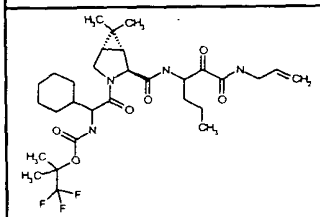
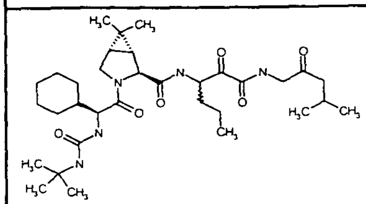
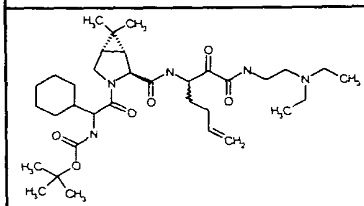
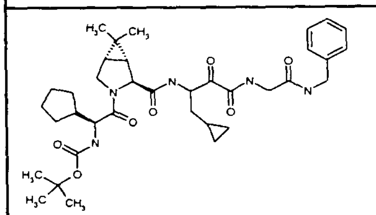
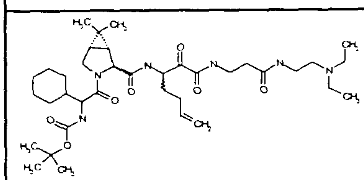
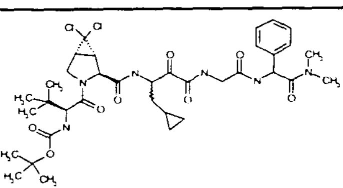
	737.95	A
	596.82	B
	547.74	B
	762.78	C
	734.73	A
	585.79	B
	694.66	A

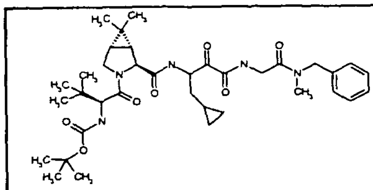
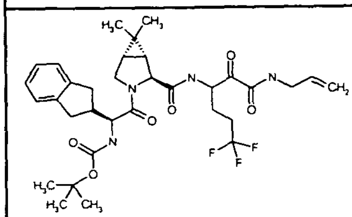
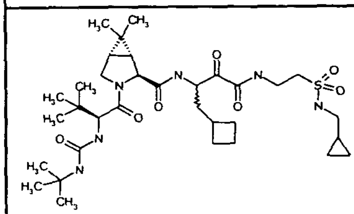
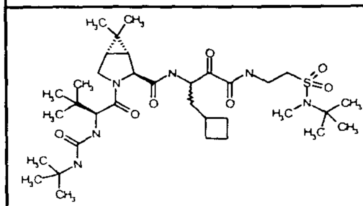
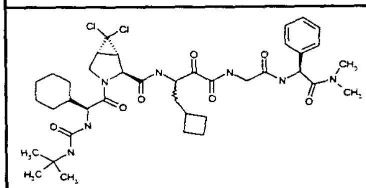
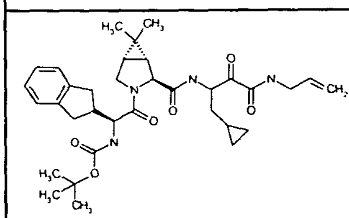
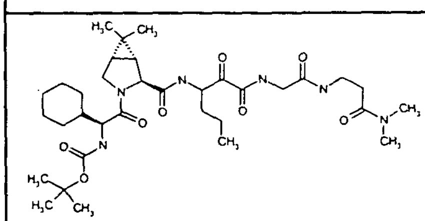
	681.88	A
	681.88	B
	680.90	B
	722.93	C
	752.96	A
	752.96	A
	752.96	A

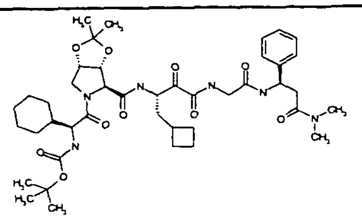
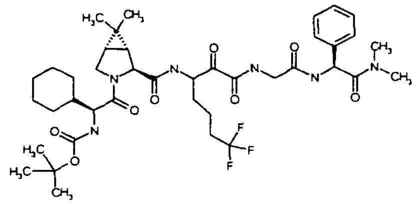
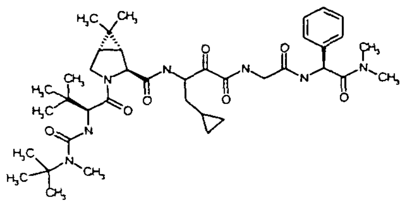
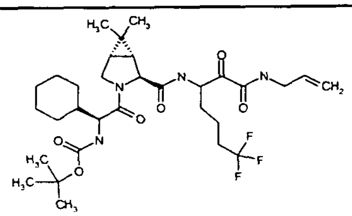
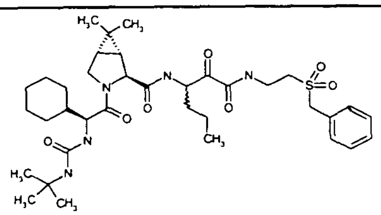
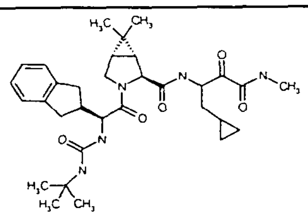
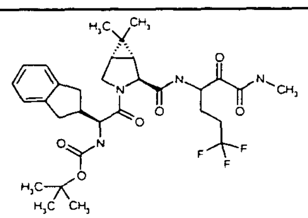
	779.00	A
	779.00	A
	779.00	A
	613.73	C
	668.68	A
	673.90	B
	629.85	B

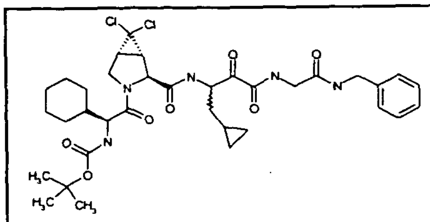
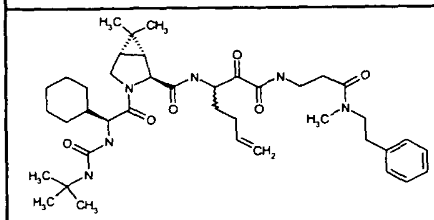
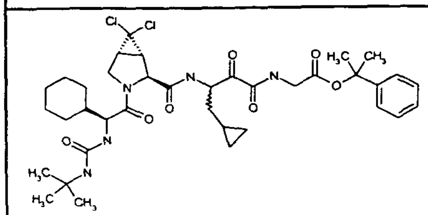
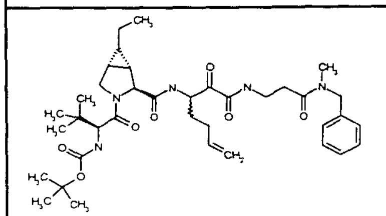
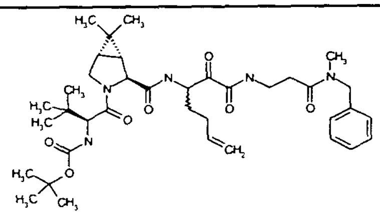
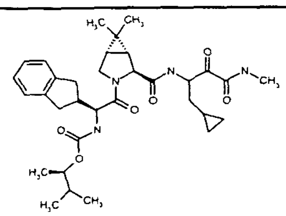
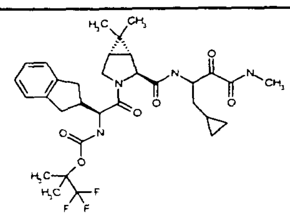
	733.74	B
	655.84	B
	655.84	B
	669.87	B
	641.52	B
	687.91	A
	615.48	A

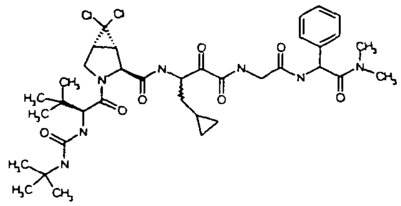
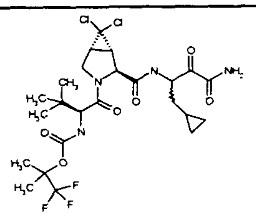
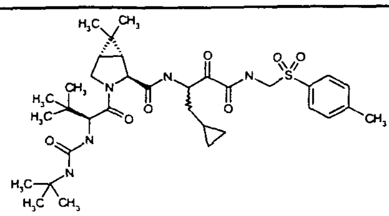
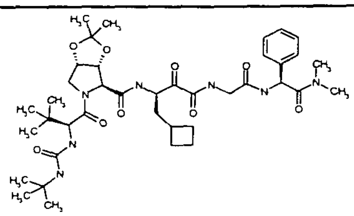
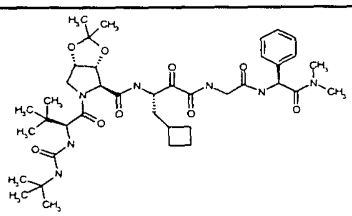
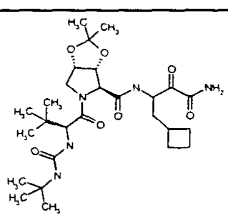
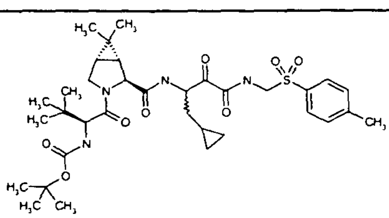
	615.48	A
	694.92	B
	707.70	A
	694.92	A
	805.81	A
	625.60	A
	640.87	B

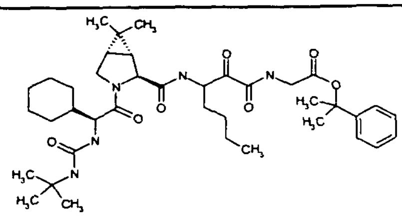
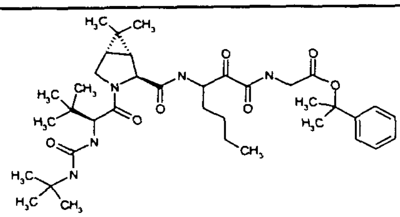
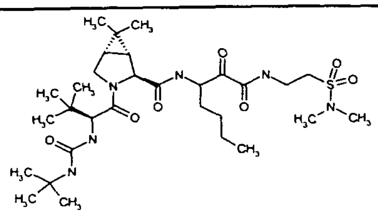
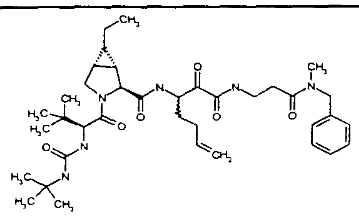
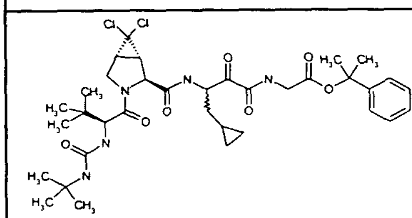
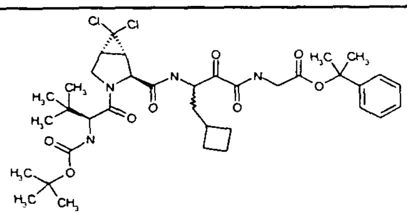
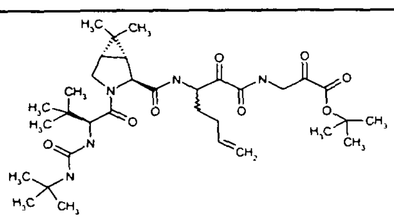
	695.91	A
	614.71	B
	617.84	B
	631.86	C
	665.84	A
	702.94	C
	765.74	A

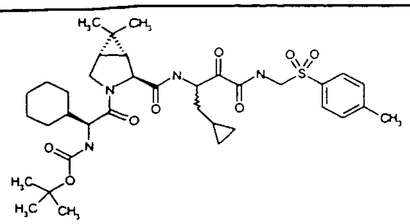
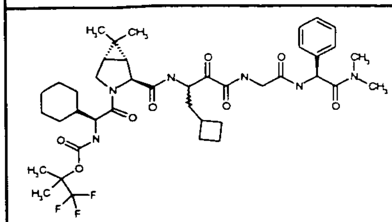
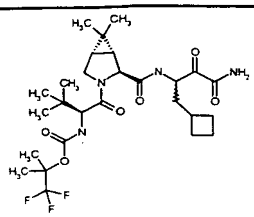
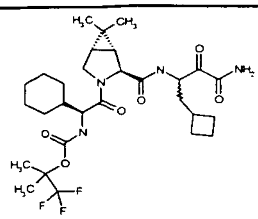
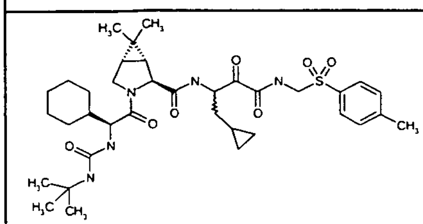
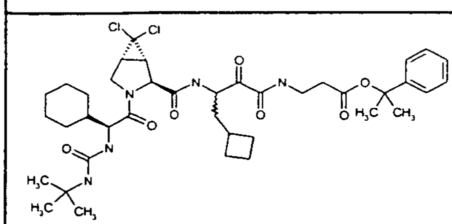
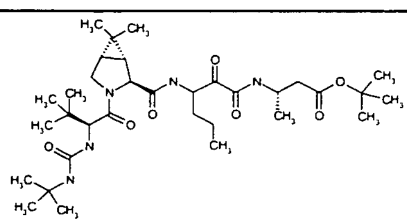
	667.85	C
	648.73	A
	680.91	B
	696.96	C
	804.82	A
	606.77	B
	676.86	A

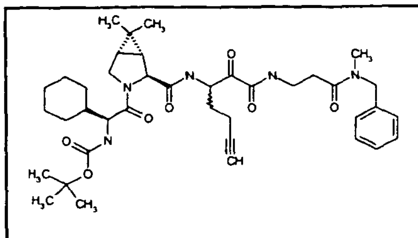
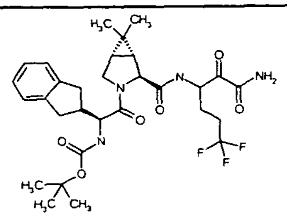
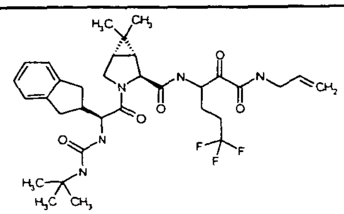
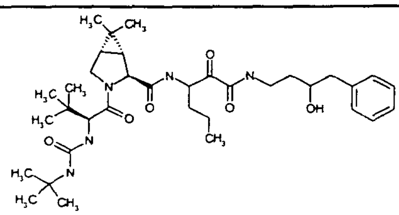
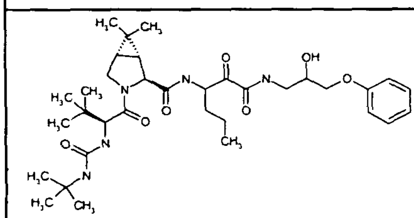
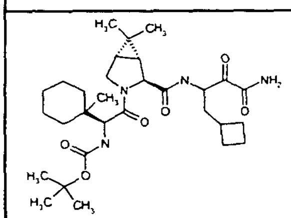
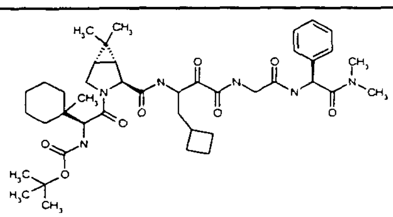
	811.00	A
	806.93	A
	737.95	A
	628.74	B
	701.93	A
	579.75	B
	622.69	B

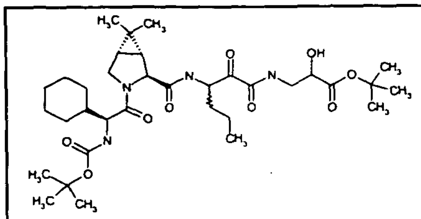
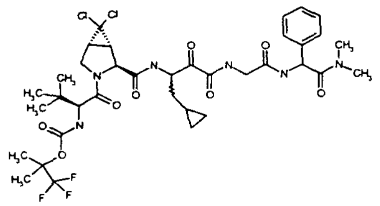
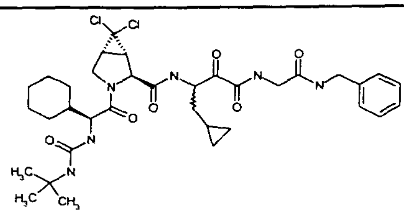
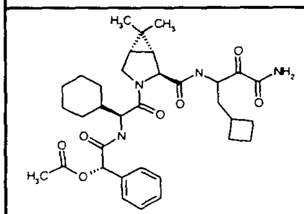
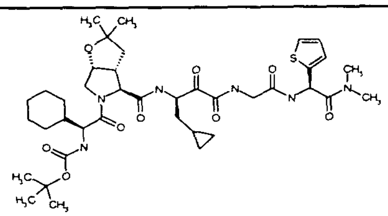
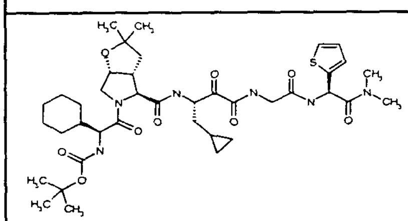
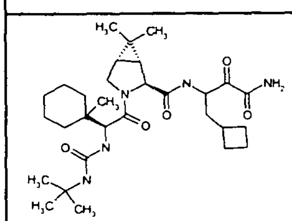
	720.70	A
	720.96	A
	748.75	A
	681.88	B
	681.88	B
	594.76	A
	634.70	A

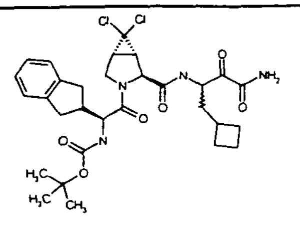
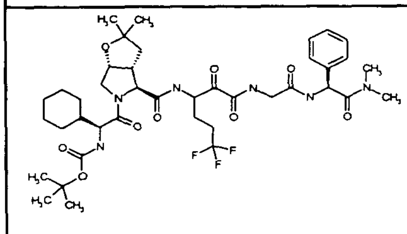
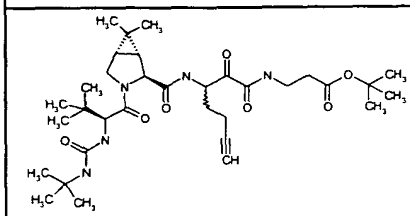
	764.76	A
	601.46	A
	673.88	A
	769.95	B
	769.95	A
	551.69	B
	674.86	B

	709.93	A
	683.90	B
	642.87	B
	680.90	B
	722.72	A
	737.73	B
	647.82	B

	700.90	A
	818.94	A
	574.65	B
	600.68	A
	699.92	B
	776.81	B
	635.85	A

	705.90	A
	608.66	A
	647.74	A
	641.86	B
	643.83	B
	560.74	B
	779.00	A

	664.85	A
	819.71	A
	719.72	A
	622.77	A
	787.00	A
	787.00	A
	559.76	A

	621.57	A
	822.93	A
	631.82	A

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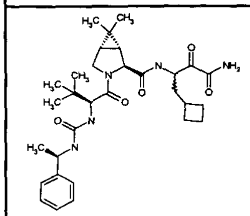
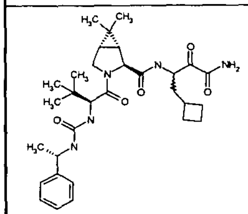
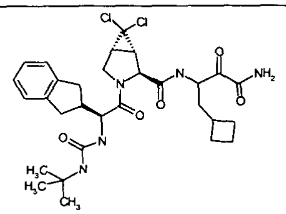
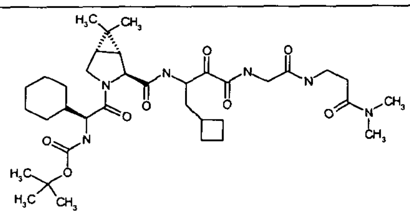
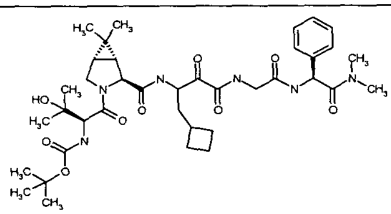
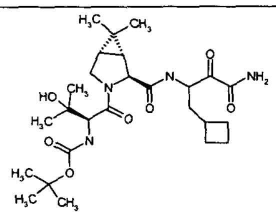
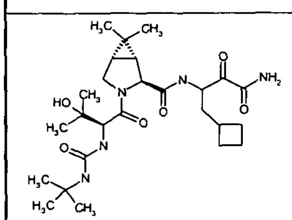
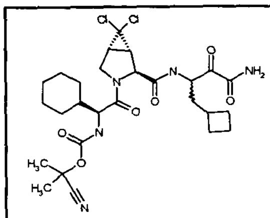
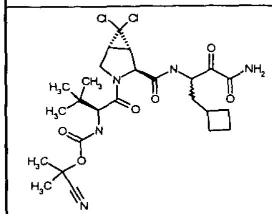
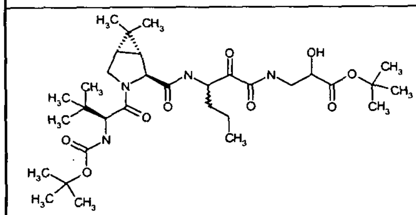
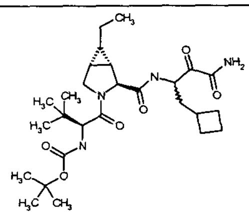
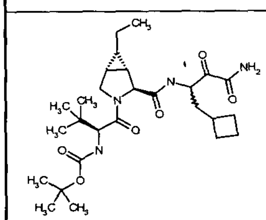
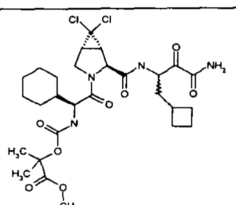
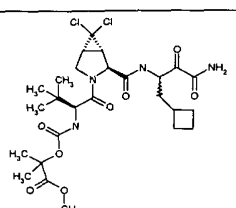
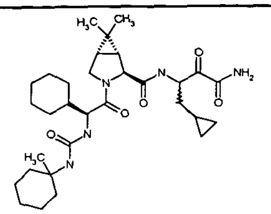
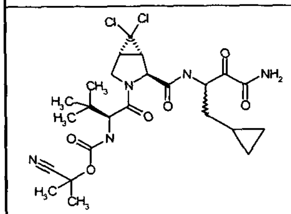
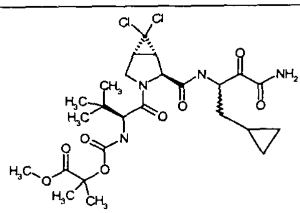
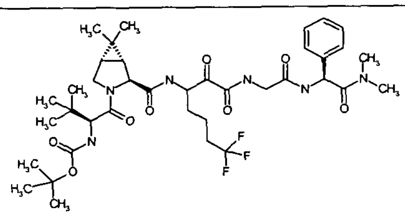
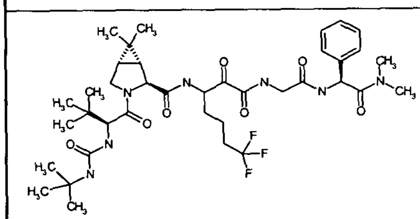
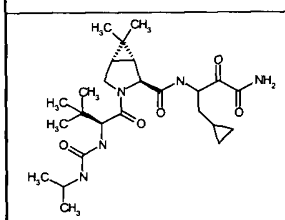
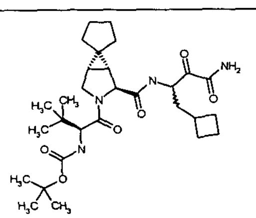
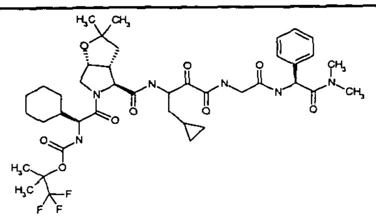
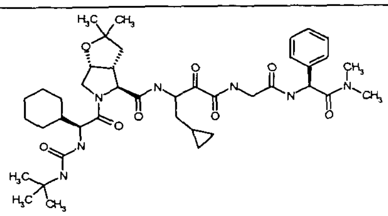
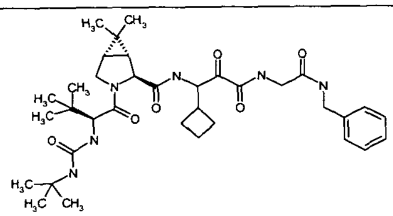
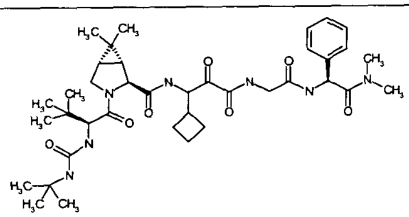
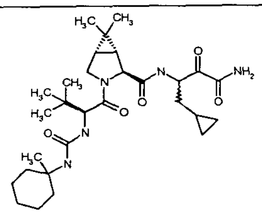
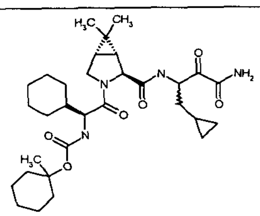
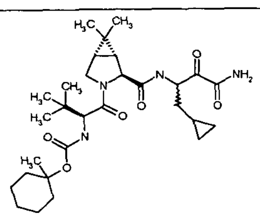
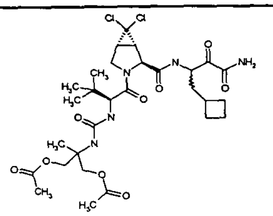
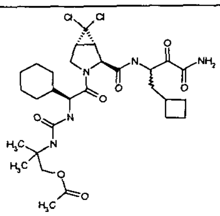
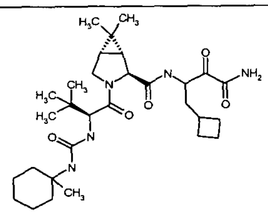
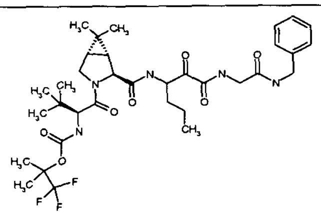
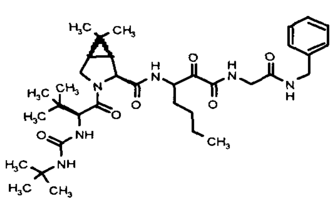
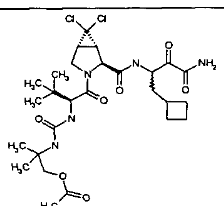
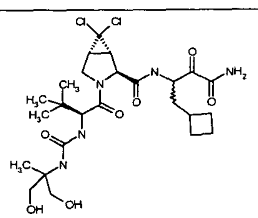
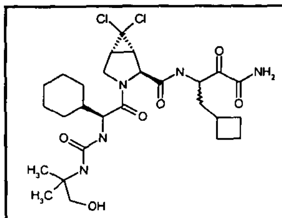
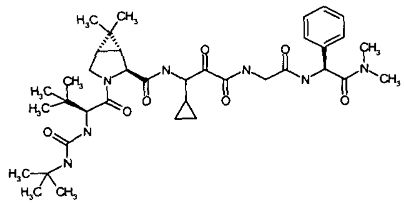
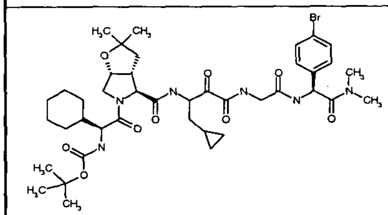
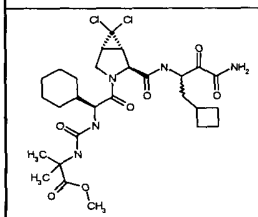
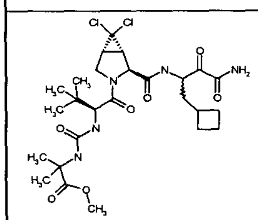
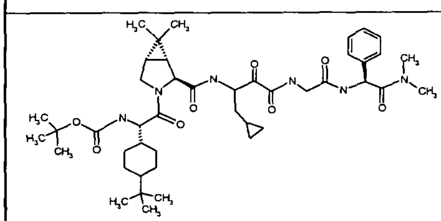
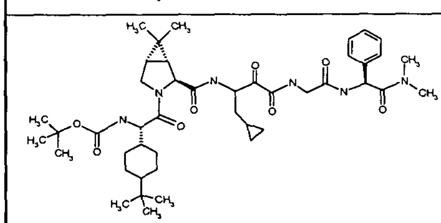
	567.74	B
	567.74	A
	620.58	A
	702.90	A
	740.91	A
	522.65	B
	521.66	B

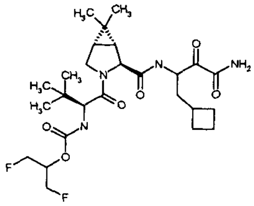
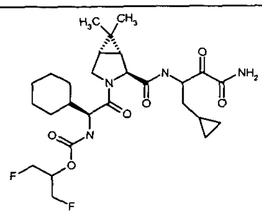
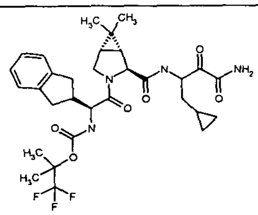
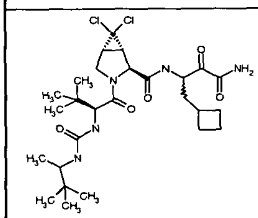
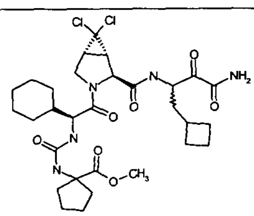
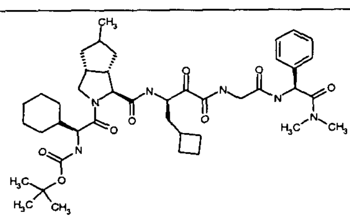
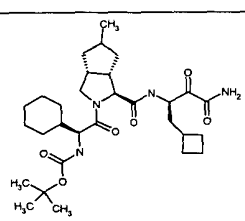
	598.53	B
	572.49	B
	638.81	B
	520.68	C
	520.68	B
	631.56	B
	605.52	B

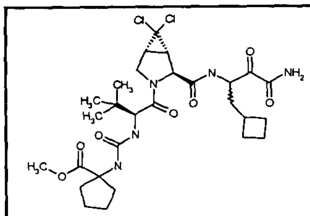
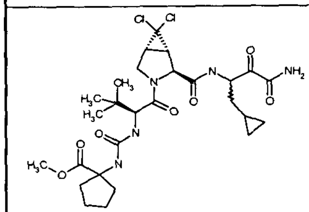
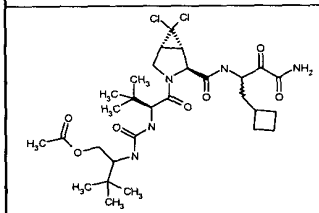
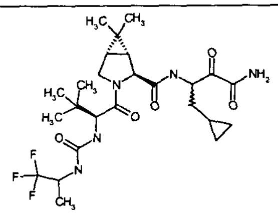
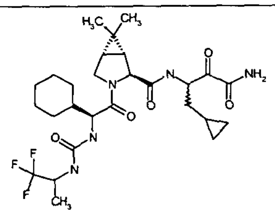
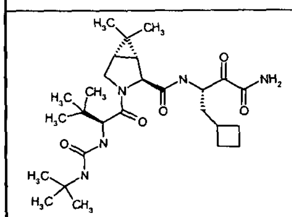
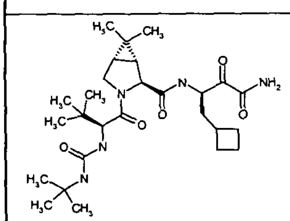
	571.77	A
	558.47	A
	591.49	A
	780.89	A
	779.91	A
	491.64	B
	546.71	B

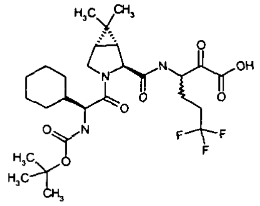
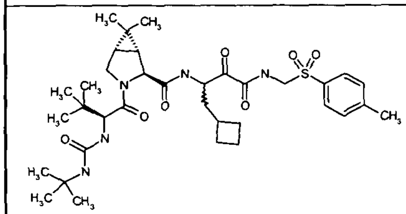
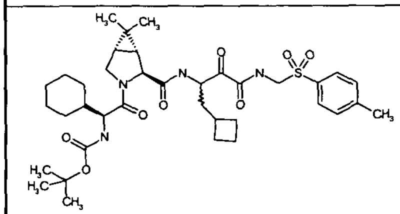
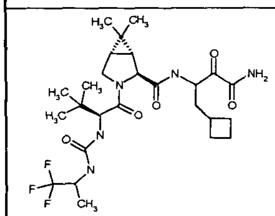
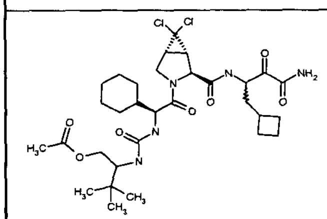
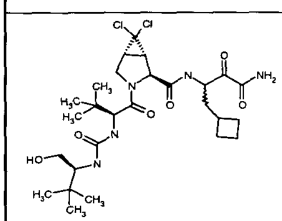
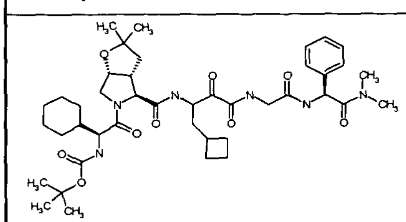
	834.94	A
	779.99	A
	652.84	A
	723.92	A
	545.73	A
	572.75	A
	546.71	A

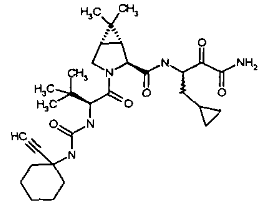
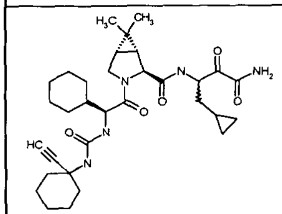
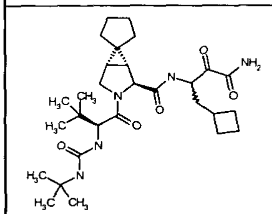
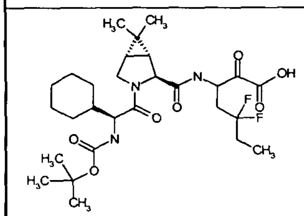
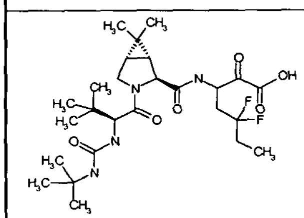
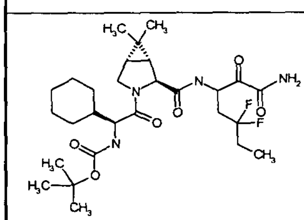
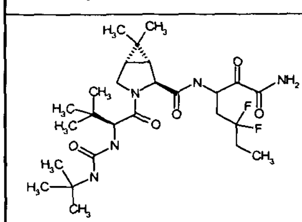
	676.60	B
	644.60	B
	559.76	A
	695.79	A
	654.86	A
	618.56	B
	592.53	B

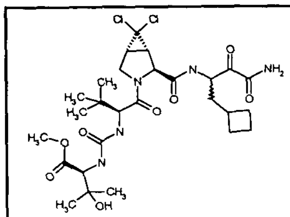
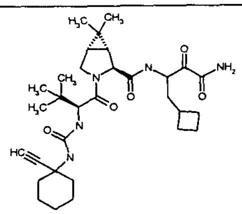
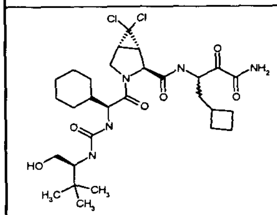
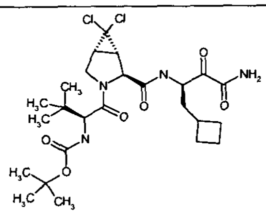
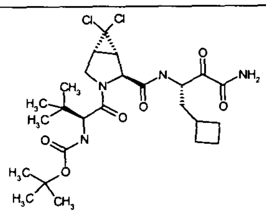
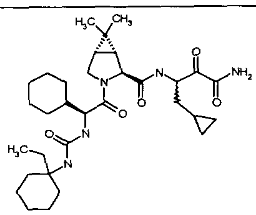
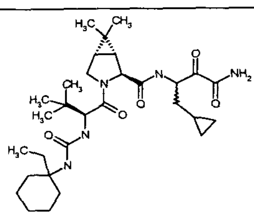
	602.56	B
	709.89	A
	859.87	A
	630.57	A
	604.54	A
	807.05	A
	807.05	A

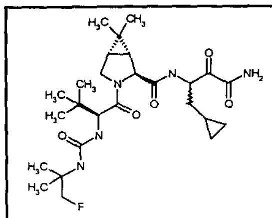
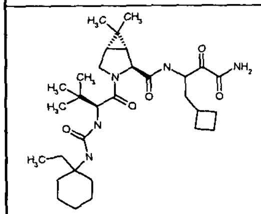
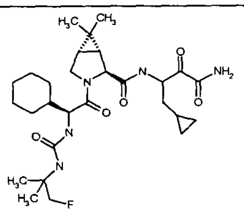
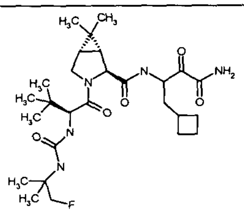
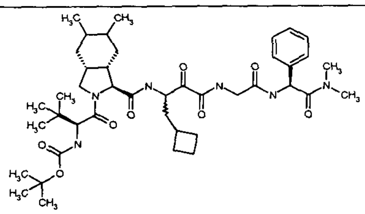
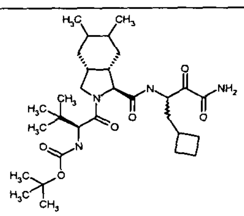
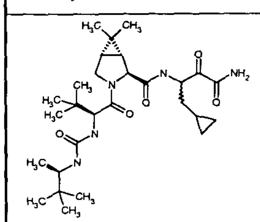
	542.63	B
	554.64	A
	620.68	A
	588.58	A
	656.61	B
	779.00	A
	560.74	B

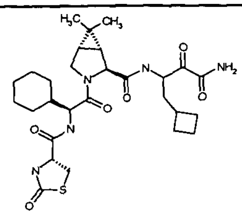
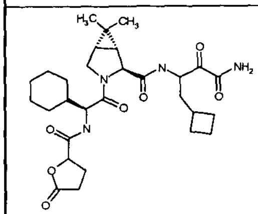
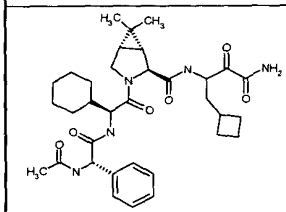
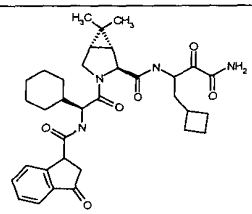
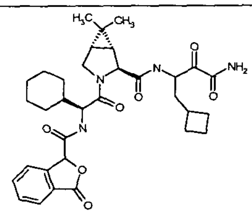
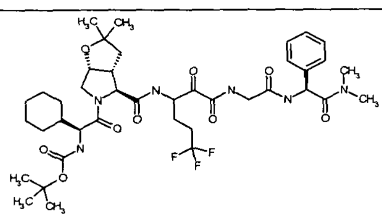
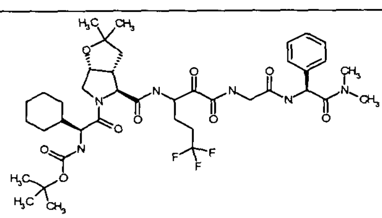
	630.57	B
	616.55	B
	646.62	A
	545.61	B
	571.65	B
	519.69	A
	519.69	B

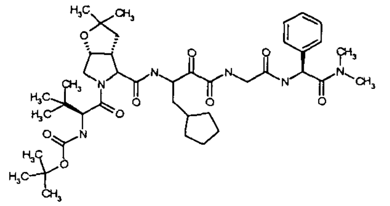
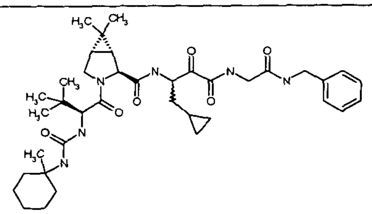
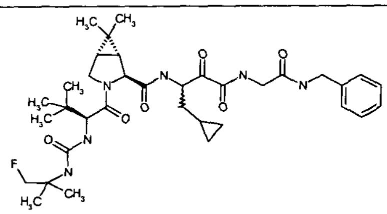
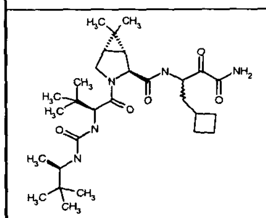
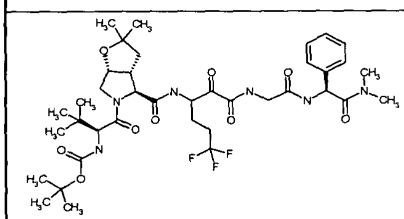
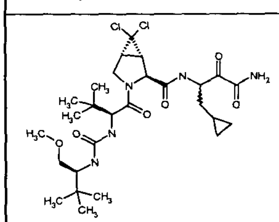
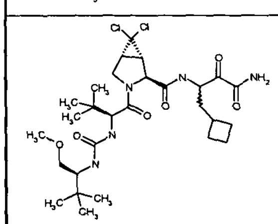
	575.63	A
	687.91	B
	714.93	B
	559.63	A
	672.66	A
	604.58	B
	795.00	A

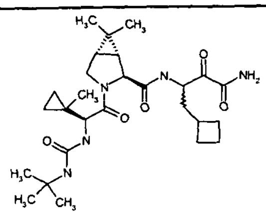
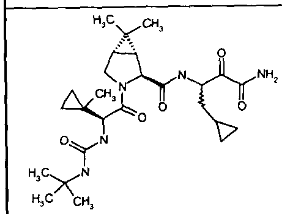
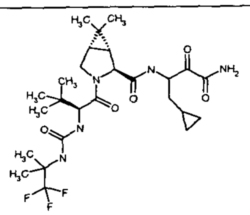
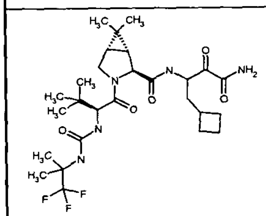
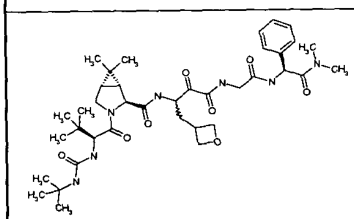
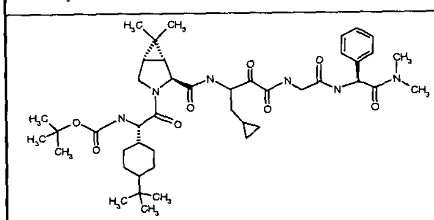
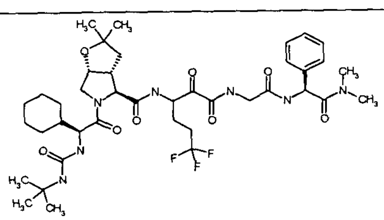
	555.72	A
	581.76	A
	545.73	B
	571.67	B
	544.65	B
	570.68	B
	543.66	B

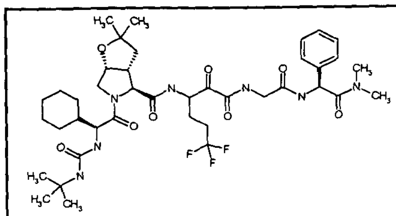
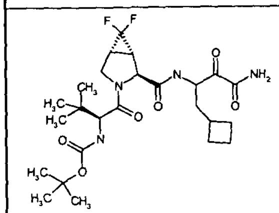
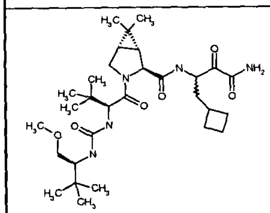
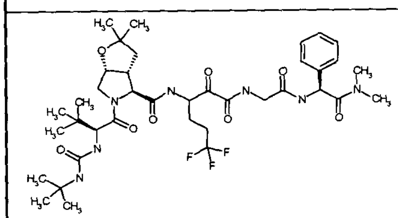
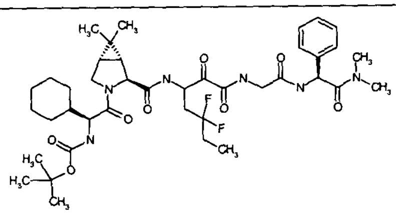
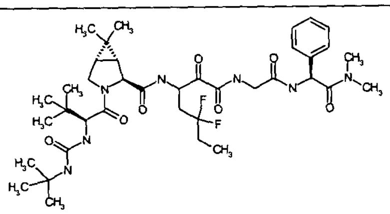
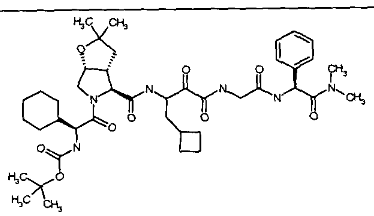
	634.56	B
	569.75	A
	630.62	B
	561.51	C
	561.51	A
	585.79	A
	559.76	A

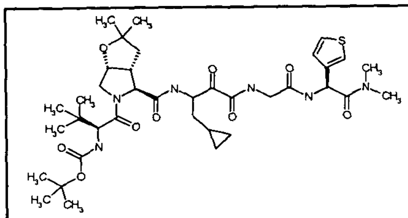
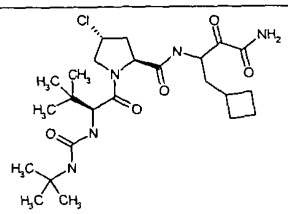
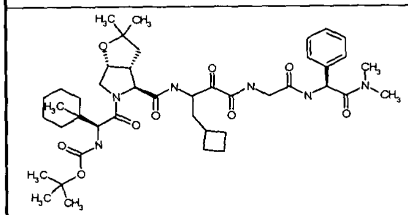
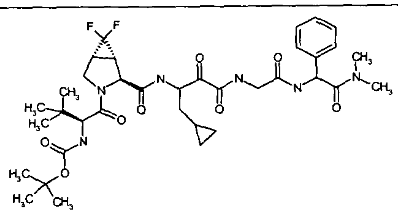
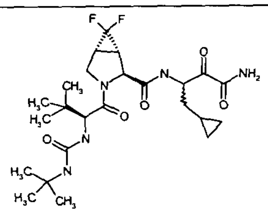
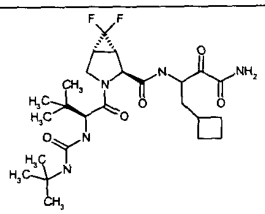
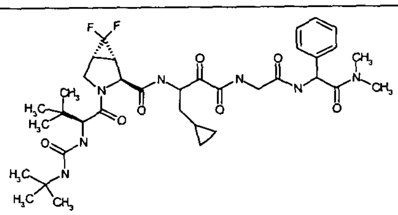
	523.65	A
	573.78	A
	549.69	A
	537.68	A
	781.01	A
	562.76	B
	533.72	A

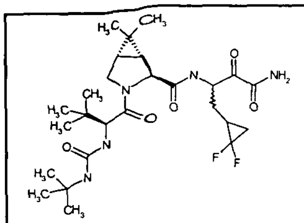
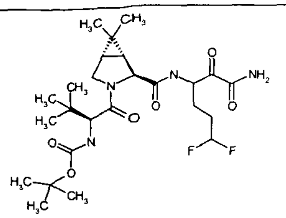
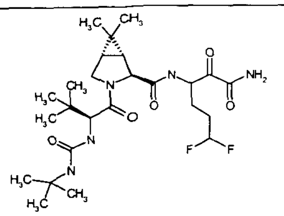
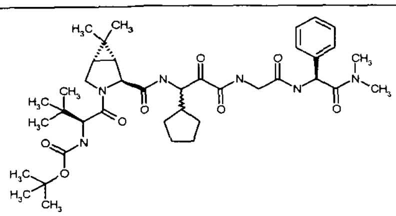
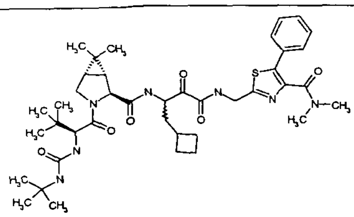
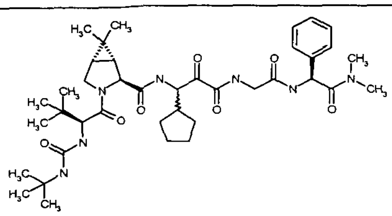
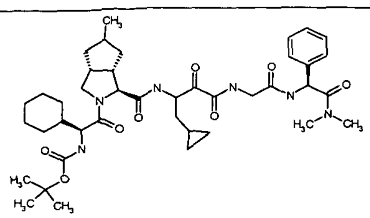
	575.73	A
	558.68	A
	621.78	A
	604.75	B
	606.73	A
	822.93	A
	822.93	A

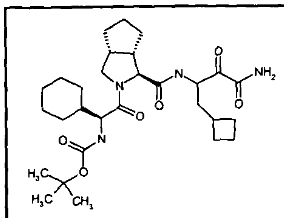
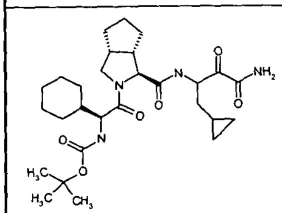
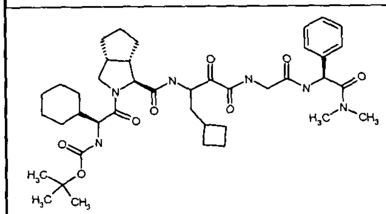
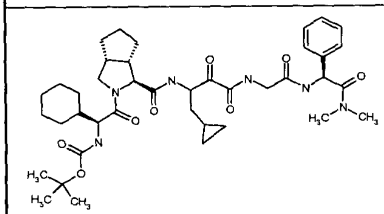
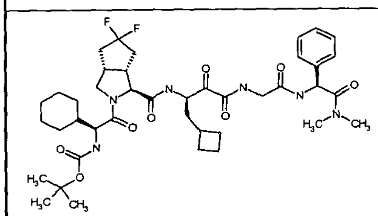
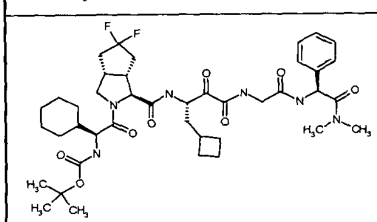
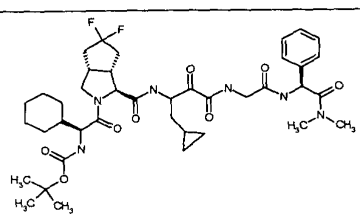
	782.99	A
	692.91	A
	670.83	A
	547.74	A
	796.89	A
	604.58	A
	618.61	A

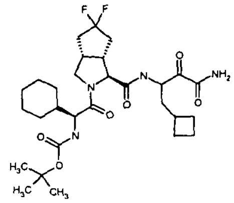
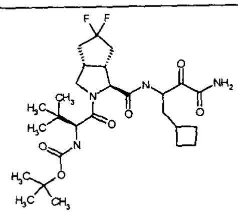
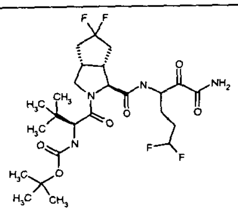
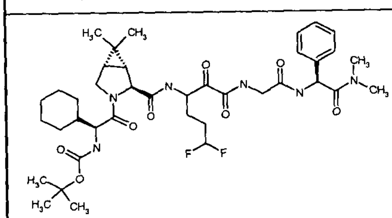
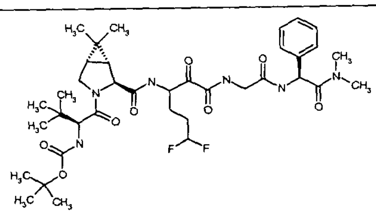
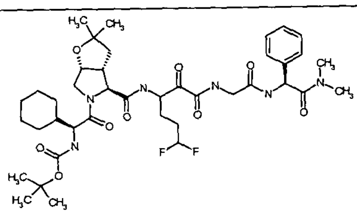
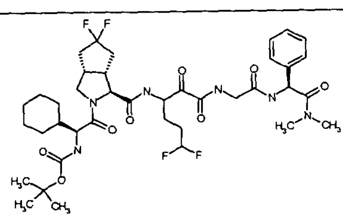
	517.67	B
	503.65	B
	559.63	A
	573.66	A
	739.92	A
	807.05	A
	821.95	A

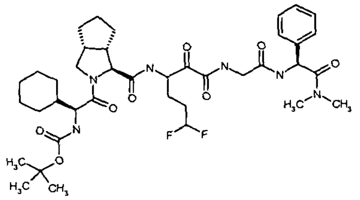
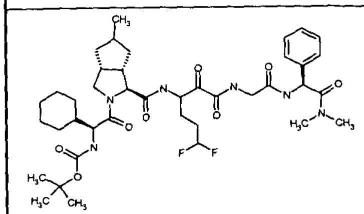
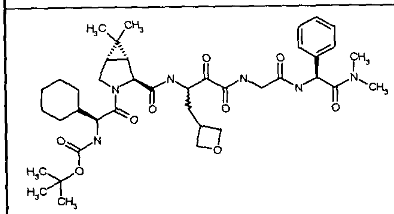
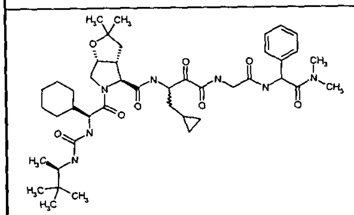
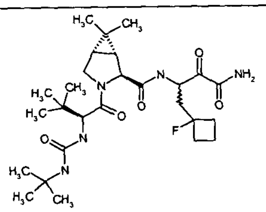
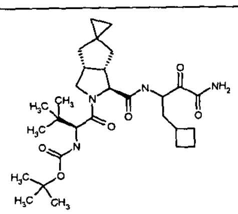
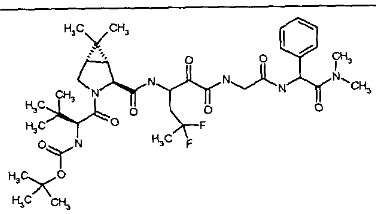
	821.95	A
	528.60	B
	577.77	B
	795.91	A
	788.94	A
	761.92	A
	795.00	A

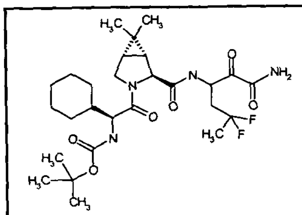
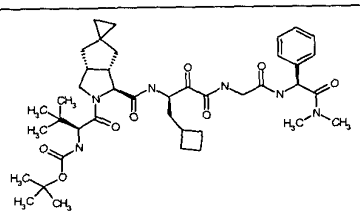
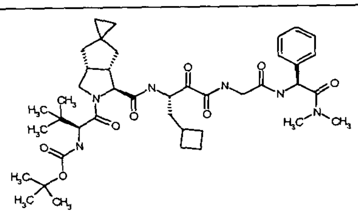
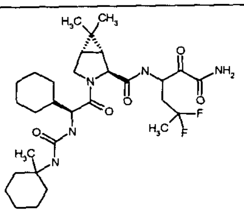
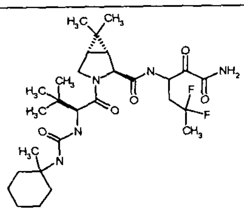
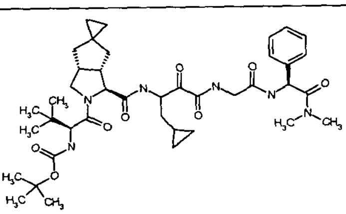
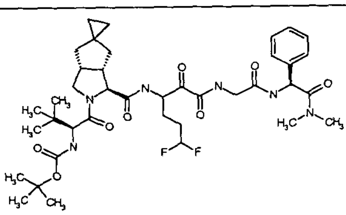
	760.96	A
	514.07	B
	809.02	A
	732.83	A
	513.59	B
	527.62	B
	731.85	A

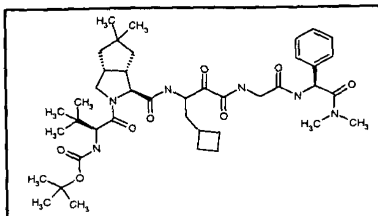
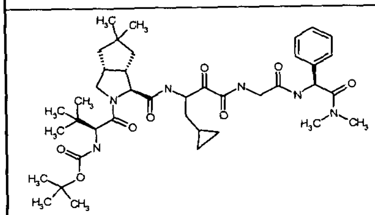
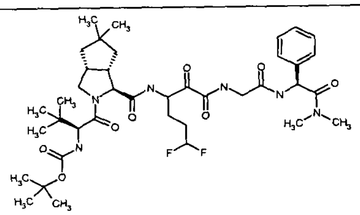
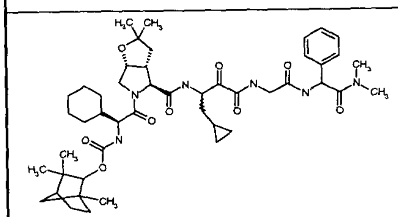
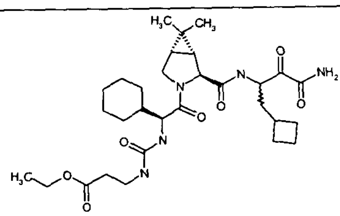
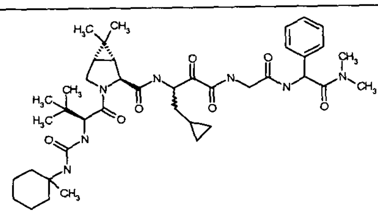
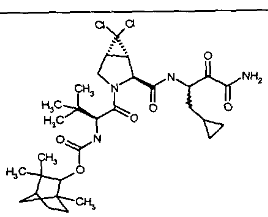
	541.64	A
	530.62	B
	529.63	B
	738.93	A
	764.01	B
	737.95	A
	764.97	A

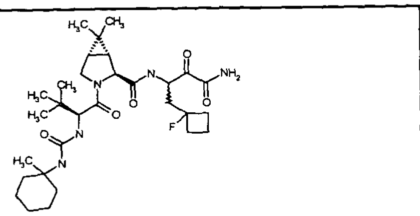
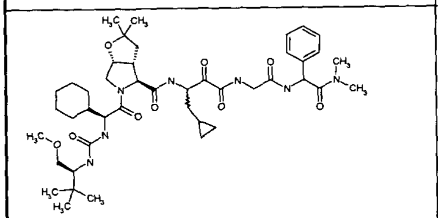
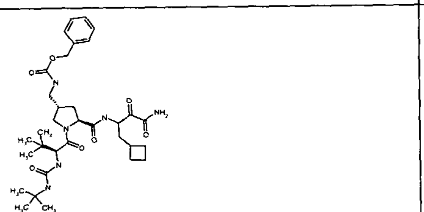
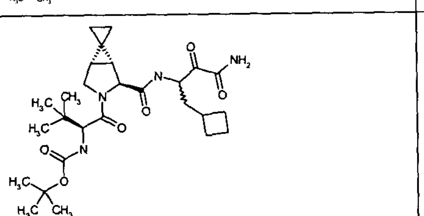
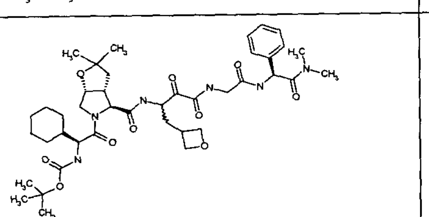
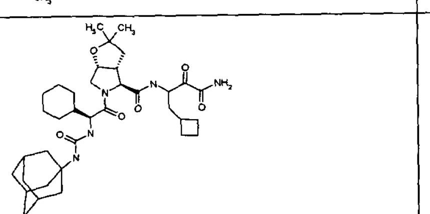
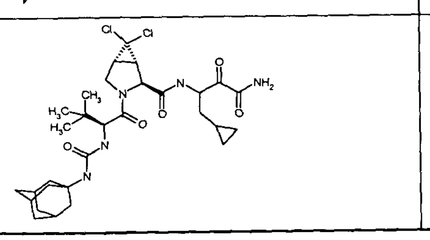
	546.71	B
	532.69	B
	764.97	A
	750.94	A
	800.95	A
	800.95	A
	786.92	A

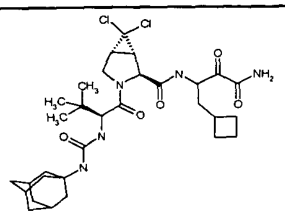
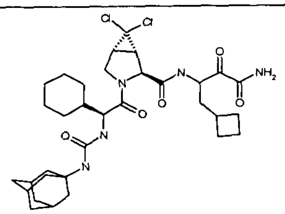
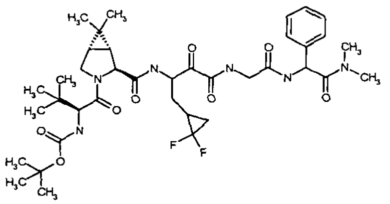
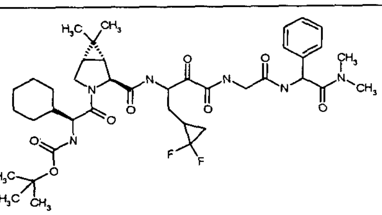
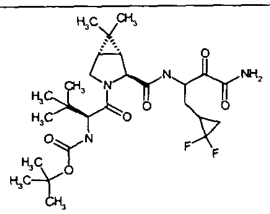
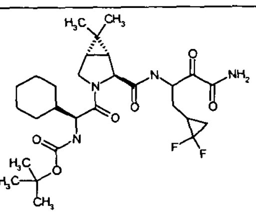
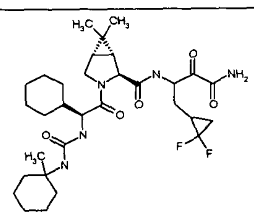
	582.69	B
	556.66	B
	566.60	B
	774.91	A
	748.88	A
	804.94	A
	810.89	A

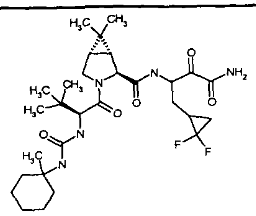
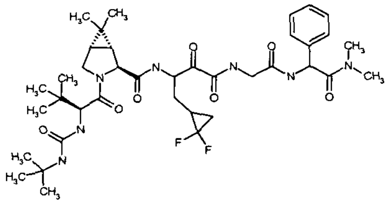
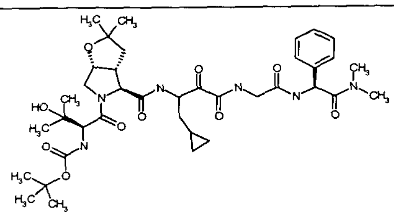
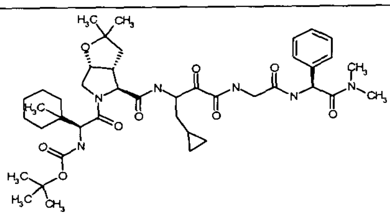
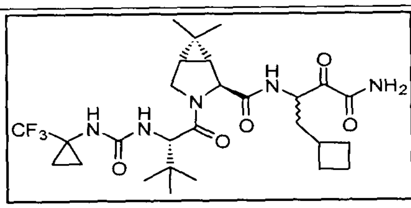
	774.91	A
	788.94	A
	766.94	A
	808.04	A
	537.68	B
	546.71	B
	748.88	B

	556.66	B
	764.97	B
	764.97	A
	595.74	B
	569.70	A
	750.94	A
	774.91	A

	766.99	A
	752.96	A
	776.93	A
	861.10	A
	589.74	A
	763.99	A
	627.61	A

	577.75	A
	838.07	A
	642.80	B
	518.66	B
	796.97	A
	653.87	B
	624.61	A

	638.64	A
	664.68	A
	760.89	A
	786.92	A
	542.63	A
	568.67	A
	607.75	A

	581.71	A
	759.90	A
	756.90	A
	795.00	A
	571.63	A